MULTIPLE PRIMARY TUMOURS IN HEAD AND NECK CANCER: AN EPIDEMIOLOGICAL STUDY

INGEBORG J.M. DHOOGE

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Prof. dr. F.W.J. Albers

...je zult geboren worden met een gladde handpalm, maar enkele uren nadat je geboren bent zal die ongerepte oppervlakte zich vullen met tekens, lijnen, voorspellingen: je zult sterven met een dicht net van dorre lijnen in je hand, maar enkele uren nadat je gestorven bent zal ieder spoor van een lotsbestemming uit je handen verdwenen zijn ...

Carlos Fuentes

Aan mijn ouders

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CHAPTER 1

INTRODUCTION AND DEFINITIONS

Multiple primary tumours in head and neck cancer: etiology and incidence.
IJ Dhooge, FWJ Albers
JBR-BTR 1994; 77: 55-59

Epidemiology and etiological factors of laryngeal cancer.
PB Van Cauwenberge, IJ Dhooge, KJ Ingels
Acta ORL Belg 1992; 46: 99-102

INTRODUCTION

The average annual rate of squamous cell carcinoma of the upper aerodigestive tract in Belgium is 22.4/100,000. It accounts for approximately 3.5% of all malignant neoplasms in our country (1). World-wide more than 500,000 new cases are registered annually and this incidence shows a tendency to increase (2,3). Although treatment protocols of head and neck cancer have improved considerably over the last 20 years, the overall survival rate has only marginally increased (4). Though better methods of controlling local and regional disease have been developed, the occurrence of second primary tumours has become increasingly responsible for the lack of progress (5,6).

« So ist wohl auch die Annahme nicht auszuschliessen, dass, bei einem Individuum sich zweimal im Leben Carcinom entwickeln kann, wenn das erste mal radikale Heilung durch die Operation erzielt worden war.» So concluded Theodore Billroth his report, more than a century ago, of what were probably the first clearly documented examples of multiple primary malignant neoplasms (7). More than 60 years later, in 1932, Warren and Gates reviewed 1259 patients from the world literature (7). In their report they proposed the classification criteria for second primary tumours that are at present still used (see Def.2, below). Since then, many studies have been published reporting a rising incidence of multiple primary tumours. By careful and detailed histological studies, Slaughter and co-workers demonstrated in 1953 the phenomenon of multicentricity in patients with squamous cell cancer of the oral epithelium. They realised that the entire epithelial surface at risk is exposed to repeated carcinogenic insults (e.g. from tobacco use) and suggested that such exposure increases the likelihood that multiple, independent premalignant and malignant foci will develop in the exposed epithelium (8). Squamous cell carcinoma of the oral cavity is then the end result of a process of «field cancerization». This led to the concept of a large zone of mucosa at risk, the so-called «condemned mucosa». Better understanding and greater awareness led to increasing incidence reports. The occurrence of multiple primary carcinomas is especially important in head and neck cancer. Ogden et al. showed that patients with head and neck cancer have a greater risk of a second primary malignancy than any other group of patients with cancer (9). Multiple primary malignancies, once considered a medical rarity, are today considered a common problem in head and neck oncology.

DEFINITIONS

1. Criteria

It is essential to define the criteria used to diagnose multiple primary malignancies in order to differentiate a second primary lesion from a primary tumour with metastasis. In 1932, Warren and Gates redefined the original criteria of Billroth as follows (7):

1. Each tumour must be clearly malignant on histological examination.
2. Each tumour must be geographically distinct and not connected by submucosal or intraepithelial neoplastic changes.
3. The possibility of the second tumour representing a metastasis must be excluded.

The fulfilment of criterium 2 is not always evident. When the separate foci have significant histological differences, the diagnosis of separate primary cancers is appropriate. But when both tumours have the same histology, other microscopical findings are important. Probably the most important histological observation of a separate primary infiltrating carcinoma is identification of its origin from the overlying epithelium. The observation that the invasive carcinoma arises from an overlying epithelium that demonstrates a transition of carcinoma in situ to invasive carcinoma is proof for a primary tumour. Often, the pathologist can differentiate a metastatic lesion from a separate primary tumour by microscopic examination. Still, in many cases, only probability diagnosis can be made. To overcome this difficulty, a slight modification of the second criterium was proposed by Hong et al.: «A second primary tumour of the same histologic type as the first must be separated from it by more than 2 cm of normal epithelium or must occur at least three years after the diagnosis of the first primary tumour» (10).

About criterium 3, some remarks have to be made. Distinguishing a second primary lung tumour from a metastatic lung lesion is not always clear-cut. When there are multiple lung lesions, the likelihood of a metastasis is high. Cahan stated that if a patient had or has a squamous carcinoma elsewhere in the body, a solitary lung lesion has a 3.5 to 1 chance to be a separate primary lung cancer rather than a single metastasis (11). Important considerations are:

1. The magnitude and aggressivity of the primary tumour: as a rule a solitary tumour in the lung can be regarded as a primary malignancy if the head and neck index tumour is/was classified as T1 or T2, without lymph node metastasis or without signs of local or regional recurrences (12).
2. The time interval between the detection of the primary tumour and the appearance of the lung lesions: 93% of the distant metastasis appear in the first two years following the detection of the primary tumour. The longer the time interval, the more likely it is a second primary lung tumour.
3. The localisation of the lung tumour: endobronchial versus parenchymal. Metastatic lung lesions are more frequently encountered in the lung parenchym.

Again Hong et al. suggested a more rigorous criterium: «Any new tumour of the lungs must be solitary and histologically distinct from the primary tumour, unless it occurs three or more years later» (10).

2. Classification according to time of appearance

The temporal sequence of the appearance of multiple tumours was emphasised in 1964 by Moertel, who formulated the criteria for synchronous and metachronous lesions (13).

The *index tumour* is defined as the first head and neck tumour diagnosed.

Simultaneously developing tumours are lesions which develop at the same time and are diagnosed at the initial presentation. The more malignant or more life-threatening tumour is usually called the «first» or «index» tumour.

Synchronous tumours include those that present either simultaneously or within a 6 month period of identification of the original tumour.

Metachronous tumours are identified as tumours diagnosed more than 6 months after the index tumour.

3. Classification according to localisation

Multiple primary tumours can be categorized according to localisation. Kapsinow, in 1962, proposed the following categories (14):

Multicentric tumours: tumours occuring in the same organ

Systemic tumours: tumours localized in anatomically or functionally allied organs of the same system e.g.the combination of a laryngeal and a lung tumour.

Paired tumours: tumours localized in bilateral organs e.g. bilateral tonsil, ovary, breast and testicular tumours.

Randomly localized tumours: coincidental associated tumours e.g. laryngeal and bowel carcinomas.

A fifth category was proposed by De Vries (15):

Etiologically related tumours: tumours caused by a shared etiology e.g. the combination of laryngeal and bladder cancer, which are both related to the use of tobacco.

ETIOPATHOGENESIS

1. Concept of multicentricity

The concept of multicentric origin of malignant neoplasms was already expressed in 1944 by Willis who stated:

«In human as in experimental carcinogenesis the effective stimuli are applied, not to

one cell or one small group of cells, but to a more or less extensive area of epithelial tissue. All the epithelium in that area is acted upon similarly, though of course usually not equally. Neoplasia will commence where the stimuli have been maximal, but the neoplastic response will later be manifested by neighbouring tissue that was subjected to the same original stimuli» (16).

Carcinogenesis is not an isolated biological event. It is the result of specific carcinogenic influences acting on susceptible tissue for a sufficient amount of time to start irreversible anaplastic changes in the reproductive pattern of the cells. After a variable amount of time, multiple areas of in situ carcinomatous change will begin at the point of maximum carcinogenic stimulus. Multicentricity is known in all organ systems albeit with varying frequency. In 1977, Moertel reported on the patient data collected at the Mayo Clinics. Multicentric tumours at a macroscopic level could be detected for different sites with a frequency varying from 2.2% for stomach cancer to 58% for vulva and vaginal cancer with 8.7% for oral cancer (17). At microscopic level the problem is even more impressive. Table 1 shows anatomo-pathological studies in which, during careful histological examination of macroscopic normal tissue in the vicinity of invasive cancer, separate areas of carcinoma in situ or early invasive cancer were found. The incidence of multicentricity in these studies varies between 20% for cancer of the vulva and 93% for oral cavity cancer.

Table 1: Frequency of multicentric tumours in tissue studies of patients with an invasive tumour in the same organ (after Moertel, Cancer 1977;40:1786-92)

Author, Year	Site	%
Green et al. 1958	Vulva	20
Collins and Gall 1952	Stomach	22
Skinner et al. 1974	Bladder	56
Auerbach et al. 1957	Lung	89
Slaughter et al. 1946	Oral cavity	93

Multicentric, systemic and paired tumours are often etiologically related. The observation that all stages of carcinogenesis may be present not only in one system but also in different areas of related systems subjected to the same carcinogens and co-carcinogens (promoting factors) has led to the concept of a larger multicentric zone. Indeed, it seems logical that the oral area, the oesophagus and the tracheobronchial area, as they are exposed to surface-contact carcinogens, will respond by forming multiple primary neoplasms, either simultaneously or metachronously. The mere existence of one tumour implies an increased susceptibility to the development of other malignant neoplasms in the same or related systems.

Information on the genetic basis of a possible multistep process of carcinogenesis is accumulating. Tumour initiation starts with somatic mutations, causing an altered expression of specific genes involved in proliferation and differentiation of squamous epithelium (18). Several groups are currently involved in the elucidation of these steps and the associated genetic and/or phenotypic alterations (19,20,21). Mutations in the p53 tumour suppressor gene represent a genetic alteration occurring during the evolution of premalignant lesions to malignancies of the upper aerodigestive tract. The discordant p53 mutations in second primary cancers arising in patients with primary epithelial cancer of the upper aerodigestive tract suggest that these cancers arise as independent events (22,23,24).

2. *Etiological factors*

Tobacco and alcohol

Tobacco and alcohol are established risk factors in the development of squamous cell carcinoma of the head and neck. The aromatic hydrocarbons of tobacco are known carcinogens to the upper and lower respiratory tract as well as to the digestive and genitourinary systems. Experimental evidence suggests a role for tobacco in the molecular progression of squamous-cell carcinoma of the head and neck (p53 mutations at nonendogenous mutation sites) (25). Increasing intensity and prolongation of smoking is associated with an increased relative risk (26,27). Quitting smoking is asociated with a sharply reduced risk of cancer of the head and neck, with no higher risk detected among those who have quit for 10 years or more (26).

Epidemiological and experimental data support the existence of an interaction between alcohol and mutagens (eg cigarette smoke condensate) and suggest that alcohol has co-carcinogenic properties (28,29). Ethanol, though itself not a mutagen, exerts its genotoxic effect by blocking repair of genetic damage induced by mutagens (28). Some studies, however, have shown that there is an independent and different contribution to the incidence of head and neck cancer for alcohol consumption (30). No consistent findings have been found on the risk of different types of alcohol, such as hard liquor, wine and beer, related to the relative risk of developing head and neck carcinoma (31). Alcohol is also believed to cause a debilitated status in the host through malnutrition and immune surveillance suppression (32).

Some studies support the hypothesis of a carcinogenic effect of alcohol and tobacco via a direct contact mechanism: tobacco smoking is more strongly associated with lesions in sites heavily exposed to inhaled smoke, whereas alcohol consumption has a stronger effect on structures belonging to the «food channel» (30,33). A dose-response relationship can be demonstrated for tobacco smoking as well as for alcohol consumption (26,33,34,35).

Irradiation

Reports on the association between irradiation and the development of metachronous tumours have been conflicting. Most authors agree that low dose radiotherapy administered for benign conditions augment the incidence of head and neck neoplasms, mostly after an interval of 30 years. There are, however, conflicting reports concerning the risk for development of a second primary tumour after a therapeutic irradiation for a malignant neoplasm of the head and neck. Some studies have shown that radiotherapy reduced the local incidence of new tumours by destroying microscopic tumours (36,37). Others report an increased risk of cancer in areas that have received therapeutic irradiation (32,34). Wagenfeld analysed his cases of stage T1 glottic carcinomas for the frequency of late recurrences and/or second primaries in the larynx following radiotherapy (38). He concluded that late recurrence and/or second primary in the larynx was not a significant problem following radiotherapy for laryngeal carcinoma.

Host factors

Copper et al. (39) and Bongers et al (40) showed in an epidemiological case-control study that a genetic predisposition is an independent risk factor for head and neck carcinogenesis. They demonstrated that first degree relatives of head and neck squamous cell carcinoma patients have a relative risk of 3.5 to develop a head and neck tumour. Cytogenetic studies, measuring the bleomycin-induced damage in cultured lymphocytes, support the existence of a constitutional risk factor for head and neck carcinogenesis (41,42,43,44). Variability in genetically determined detoxification pathways of procarcinogenic components of cigarette smoke by specific enzyme systems (eg glutathione S-transferase and cytochrome p-450 enzymes) may be important in neoplastic transformation (18). Gallo et al. showed that chromosomal analysis of head and neck cancer patients (HNCPs) with multiple tumours demonstrated a higher sensitivity to clastogens than of HNCPs with a single cancer (45). This increased mutagen sensitivity, as shown for HNSCC and especially HNSCC patients who develop a second primary tumour (SPT), could result from an inherited predisposition (41,42).

There is still a lot of discussion about the role of the immune system in the aetiology of second primary tumours. Some studies suggest that cancer patients have a generalised immunologic incompetence (32). An important observation was made by Shikhani et al. who found that patients, who have received radiotherapy, show significant decreases in total lymphocytes, T cells, helper cells, and helper/suppressor ratios (46). This long lasting radiation-induced immune depression, alone or in combination with the immune depression due to tobacco products, may have relevance to the development of second primary tumours in the head and neck. Immunologic incompetence suggests an increased risk of cancer not only in the

region of the head and neck, but in other tissues as well. Further studies are required with special emphasis on detecting high-risk groups by means of HLA or immunoglobulin typing.

Occupational factors

Occupational exposure to sulphuric acid, coal/tar products, mineral vitreous fibres, thermoplastic resins, pesticides, paint and other chemicals is a proven etiological factor in head and neck cancer (47,48). Concerning asbestos, contradictory reports have been made. Stell and McGill found an association between laryngeal carcinoma and asbestos exposure (49), while Parnes could not demonstrate asbestos as an etiological factor but only as an irritant (50). More detailed epidemiological studies which are adjusted for alcohol and cigarette consumption are necessary to investigate a possible association between occupational agents and head and neck cancer.

Nutritional factors

Epidemiological data suggest an inverse association between the consumption of fruits and vegetables and the incidence of head and neck cancer (51,52). From epidemiological and animal studies it became evident that some micro-nutrients are protective against cancer. Examples are selenium, vitamin E, and vitamin A (53). Retinoids, the synthetic and natural vitamin A derivatives, may play a major role in the prevention of progression of premalignant lesions that are often found in head and neck carcinoma patients.

AIMS OF THE STUDY

Most early reports on multiple primary cancers of head and neck were retrospective studies reporting incidences varying from 2% to 30%, with an average of 5%. This knowledge resulted in prospective studies looking for synchronous and metachronous multiple primary tumours. As was expected, in prospective studies incidences of synchronous tumours were even higher. To have a better idea of the magnitude of the problem, we performed a meta-analysis on data from 25 studies reporting synchronous and metachronous malignancies in head and neck cancer patients (Chapter 2). We wanted to answer the following questions:

1. What is the prevalence of synchronous and metachronous second tumours?
2. Does the prevalence of multiple primary tumours depend on the site of the index tumour?
3. Does the site of the second tumour depend on the site of the index tumour?

Demographic variations in patterns of head and neck malignancies imply that the incidence of multiple primary tumours published in literature cannot unquestionably be extrapolated to different countries. Therefore we conducted a prospective study of patients with head and neck malignancies undergoing treatment and follow-up at the Department of Otorhinolaryngology at the University Hospital of Ghent.

In Chapter 3 the epidemiological data of the 127 patients are outlined.

In Chapter 4 we describe the results of the panendoscopic procedure used as a screening for synchronous primary tumours. We wanted to answer the following questions:

1. What is the incidence of simultaneous primary tumours of the head and neck in our population?
2. Is it necessary to perform a panendoscopic procedure in every head and neck cancer patient as a screening procedure for simultaneous primary tumours?

In Chapter 5 we evaluate the usefulness of the rigid bronchoscopy and bronchial washings in detecting a synchronous primary lung tumour in the presence of a squamous cell carcinoma of the head and neck

In Chapter 6, we report the results of the follow-up of the 127 patients. We specifically looked for:
1. The incidence of synchronous and metachronous second primary tumours

2. The implications of the appearance of a second primary tumour on survival.

Finally, future perspectives concerning follow-up and treatment of head and neck cancer patients are discussed.

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CHAPTER 2

MULTIPLE PRIMARY TUMOURS IN HEAD AND NECK CANCER: A META-ANALYSIS.

Multiple primary tumours in head and neck cancer: a meta-analysis.
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Submitted

ABSTRACT

Head and neck cancer is often associated with second primary neoplasms, the incidence varying from 5% to 30%.
A meta-analysis was performed on data from 25 studies reporting synchronous and metachronous second malignancies in head and neck cancer.
The overall prevalence of multiple primary tumours is 15.2%. The prevalence of synchronous second primaries in prospective studies is higher than in retrospective studies (9.05% vs 4.5%). Site analysis shows that the prevalence and the localisation of second malignant tumours depended on the site of the index tumour. Oral cavity cancer has the highest prevalence of second malignant tumours. Head and neck second primaries were most common in this group. Laryngeal cancer patients carried the highest risk for the development of a second primary in the lung. About half of the second primaries were detected within two years after the detection of the index tumour but they continued to appear even after 5 years.
It can be concluded that multiple primary tumours are an important phenomenon in head an neck cancer. If we want to improve the long-term survival of these patients we must address to this problem.

INTRODUCTION

Treatment protocols in head and neck cancer patients have improved considerably over the last 50 years. Continuing advances in reconstructive surgery diminish the morbidity and allow larger tumour resections. When these surgical interventions are combined with radiotherapy, and eventually chemotherapy, there is an improvement in both local and regional tumour control. Unfortunately, there is only a modest impact on survival. Loco-regional recurrence is still the major cause of death (1), but the occurrence of new tumours in the same patient, and the development of distant metastases become also important in jeopardizing the survival of head and neck cancer patients (2,3,4). The overall incidence of distant metastases has not changed much, but whereas distant metastases were almost always preceded by neck metastasis in the past, this is not always the case anymore, thanks to more effective local and regional treatment (2). But even if we could develop a strategy capable of providing a 100% cure rate, the gain in survival would remain relatively modest because some patients will develop new cancers.

In 1860, Billroth was the first to draw attention to the occurrence of more than one cancer in a patient. Seventy two years later, in 1932, Warren and Gates published an extensive review on the subject (5). They formulated three criteria that must be fulfilled for a tumour to be considered as a second primary tumour. These criteria are still valid :

1) Each tumour must be clearly malignant on histological examination.

2) Each tumour must be geographically distinct and not connected by submucosal or intraepithelial neoplastic changes.

3) The possibility of the second tumour representing a metastasis must be excluded.

In 1964, Moertel classified the tumours according to time of appearance (6) :

- *index tumour*: the original presenting tumour.
- *simultaneous tumours*: tumours that develop at the same time and are diagnosed at the initial presentation.
- *synchronous tumours*: tumours detected within a 6 month period of identification of the index tumour.
- *metachronous tumours*: tumours diagnosed more than 6 months after the index tumour.

The incidence of second malignant tumours in head and neck cancer is now a well documented phenomenon, being as high as 5-30%. Clinical evidence has accumulated to support the «field cancerization» concept or «condemned mucosa» syndrome, originally formulated by Slaughter in 1953 for cancer of the oral cavity (7): all stages of carcinogenesis may be present in different areas of the aero-digestive tract subjected to the same carcinogens and co-carcinogens, not only simultaneously but also metachronously. The mere existence of one tumour implies an increased

susceptibility to the development of other malignant neoplasms in the same or related systems. More recently, information on the genetic basis of a possible multistep carcinogenesis is accumulating (8). Increased sensitivity to carcinogens, as detected by clastogen-induced chromosome fragility, increases the risk for developing tumours (8). More evidence for the multistep carcinogenesis theory is recently provided on molecular basis. Mutations in the p53 tumour suppressor gene represent a genetic alteration occurring during the evolution of a premalignant lesions to invasive cancer of the upper aerodigestive tract. The discordant p53 mutations in second primary cancers arising in patients with primary epithelial cancer of the upper aerodigestive tract suggest that these cancers arise as independent events (9,10,11).

To have a better idea of the magnitude of the problem, we performed a meta-analysis on data from 25 studies reporting synchronous and metachronous malignancies in head and neck cancer patients. We wanted to answer the following questions:

- What is the prevalence of synchronous and metachronous second tumours?
- Does the prevalence of multiple primary tumours depend on the site of the index tumour?
- Does the site of the second tumour depends on the site of the index tumour?

METHODS AND MATERIAL

We conducted an extensive literature review in which published material was included according to the following criteria :

1. The primary topic of the study was second malignancies in head and neck cancer.
2. Data were available for synchronous, metachronous, or overall rate of second primary tumours.
3. Warren and Gates' definition of second primaries was used.
4. The index tumours could be separated into the four principal regions, i.e. the larynx, oropharynx, hypopharynx, or oral cavity. Nasopharyngeal and sinus cancers were excluded. Second primaries were identified by site, including aero-digestive tract and distant locations.
5. The number of second primaries appearing by 1 year, 2 years, and more than 5 years had to be expressed as percentages of the total second primaries detected.

Twenty five studies were appropriate for inclusion (Table 1a and 1b). This gave us a total of 21,018 patients of which 10,670 were exclusively laryngeal cancer patients. Twelve of the 25 studies were prospective and were analysed separately for prevalence.

For site analysis, we used 13 studies for laryngeal cancer (10,670 patients), 7 studies for oral cavity cancer (3,619 patients), 4 studies for oropharyngeal cancer (1,845

patients), and 6 studies for hypopharyngeal cancer (1,365 patients).
For the follow-up analysis, 7 studies qualified for inclusion.

Table 1 : Individual studies used for prevalence
1a. Retrospective

First Author (reference	year	location	n	% second prima synch.	metach	total
Gluckman (40)	79	Cincinnati	162	9.2 %	-	-
Weaver (41)	79	Michigan	124	13%	7% *	20%
Mc Guirt (42)	82	NorthCarolina	100	18%	-	-
Atkinson (43)	82	Michigan	271	10.3%	15.1%	25.5%
Hordijk (36)	83	The Netherlands	100	2%	-	-
Atkins (44)	84	Philadelphia	451	2.5%	5.%	9.5%
De Vries (45)	85	The Netherlands	100	16%	-	-
Leipzig(46)	85	Colorado	384	8.9%	-	-
Lau (47)	86	Hong Kong	105	8.5%	-	-
Schuller (48)	86	Ohio	53	11.3%	-	-
Parker (49)	88	Chicago	208	7.2%	-	-
Hordijk (50)	89	The Netherlands	141	1.4%	-	-

n: index tumour cases *synch. = synchronous* *metach. = metachronous*

1b. Prospective

First Author (reference	year	location	n	% second prima synch.	metach	total
Vrabec (30)	79	Pennsylvania	1,518	2.7	8.8	11.5
Weichert (31)	79	Cincinnatti	825	2.3	4.2	6.5
Shapshay (32)	79	Boston	150	1400%	5	19
Cohn (33)	80	Michigan	267	9.4	7.1	16.5
Maisel (34)	81	Minnesota	449	800%	9.8	17.8
Deviri (35)	82	Israel	1,66	0.8	4.2	5
Gluckman (19)	83	Cincinnati	5,337	500%	8.5	14
Hordijk (36)	83	The Netherlands	970	2.2	16.8	19
Grossman (37)	83	Milwaukee	696	5.6	10.8	16.4
Shons (38)	85	Minnesota	405	3.2	9.6	13
Shikhani(14)	86	Baltimore	1,961	4.5	5.2	9.7
Larson (12)	88	Minneapolis	875	8.2	15.4	24
Haughey (39)	91	StLouis	3,706	2.5	10.3	12.8

n : index tumour cases *synch. = synchronous*
metach. = metachronous **:only 2 years of follow-up*

STATISTICS

Nonparametric tests were used for comparing site-specific rates within and across studies with correction for sample size. A level of $p<0.05$ was regarded as significant The analysis was done with the help of the Department of Medical Informatics and the statistical package SPSS was used.

RESULTS AND DISCUSSION

1. Prevalence of multiple primary tumours in head and neck cancer.

We found an overall median prevalence of second primary tumours of 15.2%. The median prevalence for synchronous second primary tumours was 7.2%. The median prevalence for metachronous second primary tumours was 8.6% (Table 2).
A possible source of bias in the calculation of the overall prevalence was the high proportion of laryngeal cancer patients (10,670 patients) in the total head and neck cancer population (21,018). Further analysis showed that this index site has a lower rate of second primary formation than other head and neck sites.

Table 2 : Meta-Analysis : Prevalence data for synchronous, metachronous and overall multiple primary tumours

Parameter	Synchronous	Metachronous	Overall
N(n)	25 (21,018)	16 (19,665)	16 (19,665)
n'	919	1,748	2,56
Mean	7.1%	9%	15%
Mean (weighted)	4.4%	8.3%	12.2%
Median	7.2%	8.6%	15.2%
Range	0.8% - 18%	4.2% - 16.8%	5% - 25.5%

N: number of studies *n: number of patients*
n': number of patients with a second primary tumour

The prevalence rates for synchronous and metachronous multiple tumours varied between the different studies. The highest synchronous prevalence was found in a study by McGuirt, which was a prospective study in which panendoscopy was performed by a trained otolaryngologist for the detection of a synchronous double tumour (42). Separate analysis of the 12 prospective studies revealed a prevalence of 9.05% for synchronous double tumours; the prevalence in the retrospective studies was only 4.5% (Table 3). Although this difference only approached significance assessed by a Mann-Whitney U-test ($p=0.08$), it confirms a general tendency that the

prevalence of synchronous multiple tumours is higher in prospective studies, because there is an active search for synchronous multiple tumours e.g. with a panendoscopic screening protocol.

Table 3 : Meta-Analysis : Median prevalence for synchronous second primaries in prospective studies vs retrospective studies

	N	median
overall	25	7.2%
prospectivestudies	12	9.05%
retrospectivestudies	13	4.5%

p = 0.087 (Mann-Whitney U-test)
N: number of studies

The overall prevalence of metachronous tumours was 8.6%. As most of the data were collected from retrospective studies, the true incidence is probably still underestimated because of patients lost in follow-up or treated elsewhere. There also is a wide range in the rates of prevalence for metachronous multiple tumours between the different studies. The reasons for this are multiple. Some studies used a Tumour Registry for the collection of their data, which explains the large proportion of second tumours not belonging to the aerodigestive system. In other studies, the prevalence data were the result of an intensive clinical surveillance of a group of patients at risk, by a single group of physicians. Some studies were conducted by Radiation Therapy Oncology Groups that probably have a selected cancer population under treatment. Racial and regional differences could also be of importance in determining the prevalence of multiple primary tumours. Environmental or occupational factors e.g. exposure to asbestos, may attribute to the development of cancer. Also smoking and drinking habits show racial and regional differences.
Another important consideration is that the prevalence of multiple primary tumours depends on the site of the index tumour. In many studies, no information was given about the site distribution of the index tumour population. Even less information was given concerning the stage distribution. This is important because patients with T1-T2 stage tumours are more likely to be cured from their first tumour and therefore are more likely to develop a second tumour (12). So the site and stage distribution in the study population determines the prevalence of multiple primary tumours. All these factors contribute to the differences noted in the prevalence of multiple primary tumours. Nevertheless we can conclude that the occurrence of multiple primary tumours is an important observation. The overall median prevalence of 15,2% suggests a sufficiently large yield to make screening worthwhile. Prospective studies, where an active search is performed e.g. by means of a panendoscopic procedure report a higher prevalence of synchronous multiple primary tumours. In the future this would equally apply to the prevalence of metachronous multiple tumours when

in the follow-up of this population at risk a screening protocol for the early detection of second tumours will be used.

2. Site analysis of second malignant tumours by index tumour site.

For the site analysis, we classified the index tumours according the ICD-O in laryngeal cancer, oral cavity cancer, oropharyngeal and hypopharyngeal cancer. The second tumours were grouped into four categories according to their appearance in the lung, in the oesophagus, in the head and neck and elsewhere in the body (Table 4). The overall prevalences for second primaries at the four index sites differed with a trend towards a higher prevalence for the oral cavity versus other sites (Table 5). This difference was, however, not statistically significant.

Table 4 : Site analysis of second malignant tumour by index tumour site

Index tumour site	N (%)	n (%)	n' (%)	Lung (%)	Esophagus (%)	H&N	Other
Larynx	13	10,671	160 (10	445 (38.4)	53 (4.6)	215 (18.5	427 (36.8
Oral Cavity	7	3,619	561 (15.5	114 (20.3)	52 (9.3)	231 (41.2	152 (27.1
Oropharynx	4	1,845	241 (13.1	35 (14.5)	14 (5.8)	117 (48.5	65 (27.0
Hypopharynx	6	1,365	187 (13.7	40 (21.4)	14 (7.5)	73 (39.0)	49 (26.2
Total	30	17,5	2,149 (12	634 (29.5	133 (6.2)	636 (29.6	693 (32.2

N: number of studies
n: number of patients with an index tumour
n': number of patients with a second primary tumour
H&N: Head and Neck

Table 5 : Meta-Analysis : Prevalence of second primaries at the four index sites

Indexsite	Median
Larynx	12.9
Oral Cavity	17.4
Oropharynx	14.4
Hypopharynx	13.0

p = 0.52 (Kruskal-Wallis test)

Within sites for laryngeal and oral cavity index tumours, the different prevalences of second primary tumours by site were statistically significant as judged by a Friedman test performed on transformed, non parametric data (Table 6). For laryngeal primary cancer, there was a strong preference for the lung as second primary site, followed by the head and neck (p=0.0001). We also noted a high prevalence of second primary cancer outside the aero-digestive tract. A possible explanation is that laryngeal cancer is primarily a disease of the sixth and seventh decade (13). Also the prognosis is

somewhat better. So patients have the opportunity to develop second tumours in unrelated organs. In the oral cavity there was a strong statistically significant predominance of second primaries in the head and neck region, followed by the lung (p=0.005). We also noted in this group of oral cavity cancer an important percentage of oesophageal tumours. Patients with oral cancer are notoriously known for excessive use of tobacco and alcohol which often gives rise to oral field cancerisation. As it is impossible to remove all of the exposed mucosa, second and third primaries are often observed in this same area. Although it was not statistically significant because of the small numbers of studies available, the same was true for the oropharyngeal and hypopharyngeal index tumour group (p=0.09).

Table 6 : Meta-Analysis : Prevalence of second primaries by site (lung, esophagus, H&N and other) for the different subsites of the index tumour (laryngeal, oral cavity, oropharynx and hypopharynx)

Second prim. / Index site	Lung	Oesophagus	H&N	Other	
Larynx	5.19%	0.34%	2.34%	4.46%	p = 0.0001 (N=1
Oral Cavity	3.2%	1.43%	9.2%	2.63%	p = 0.005 (N=7)
Oropharynx	2.48%	0.8%	5.17%	3.71%	p = 0.09 (N=4)
Hypopharynx	2.88%	0.62%	6.12%	2.41%	p = 0.09 (N=6)
Overall	3.29%	0.62%	4.29%	3.05%	p < 0.0001 (N=3

N: number of studies
p : according to Friedman test

Based upon these findings, we can state that patients with an oral cavity index tumour have a higher overall prevalence of second primary tumours. Secondly, the site of development of the second primary tumour is related to the site of the index tumour. A tumour which has risen in the digestive tract suggests an increased susceptibility of the entire upper digestive tract, while a similar susceptibility to tumour formation seems to exist along the respiratory tract axis.

3. Analysis of second primary tumours during follow-up.

We were able to find comparable data regarding intervals before detection of second primary tumours in 7 studies . The cumulative incidence of second primaries appearing by 1 year was 25% to 60% and by 2 years 43% to 74%. After 5 years, between 7% and 42% of the second primaries still remained to be detected (Table 7). When we looked at the appearance of second primary tumours in a laryngeal index tumour population, the cumulative range appearing by 1 year was 13% to 55% and by 2 years was 21% to 78%. After 5 years 0% to 47% of second primary tumours remained to be detected (Table 8). After 5 years, up to 38 % of the second tumours in

Table 7 : Incidence of second primary tumours in time course

Author (reference)	n	n'	< 1 year cum (%)	< 2 year cum (%)	> 5 years ab (%)	time of follow-u
Haughey (39)	3,706	528	186 (35)	225 (43)	223 (42)	mean 6.3 y
Larson (12)	875	207	95 (46)	132 (64)	34 (16)	10 year retro
Vrabec (30)	1,518	114	51 (45)	68 (60)	26 (23)	9 y retro
Hordijk(36)	1,148	194	58 (30)	101 (52)	58 (30)	22 y retro
Shikhani(14)	1,961	190	113 (60)	141 (74)	13 (7)	10 y retro
Cohn (33)	267	47	27 (57)	34 (72)	5 (10)	not given
Shons (38)	405	52	13 (25)	25 (48)	12 (23)	15 y retro

n: number of patients with an index tumour
n': number of patients with a second primary tumour
cum: cumulative
ab: absolute
y: year

Table 8 : Incidence of second primary tumours in laryngeal cancer in time course

Author (reference)	n	n'	< 1 year cum (%)	< 2 year cum (%)	> 5 years ab (%)	time of follow-u
Haughey (39)	1,864	206	76 (40)	85 (41)	97 (47)	mean 6.3 y
Lundgren (51)	295	32	4 (13)	7 (30)	15 (47)	minimum 3 y
Miyahara (52)	1,389	151	31 (21)	50 (33)	71 (47)	23 y retro
Strigenz (29)	218	23	5 (22)	8 (35)	5 (22)	minimum 7y
De Vries (45)	748	104	10 (10)	22 (21)	10 (10)	mean 5y 1m
Shikhani(14)	424	51	28 (55)	40 (78)	0 (0)	mean 2.3 y
Deviri(35)	1,66	84	19 (23)	25 (30)	32 (38)	not given

n: number of patients with an index tumour
n': number of patients with a second primary tumour
cum: cumulative
ab: absolute
y: year

the laryngeal index tumour population remained to appear. In the study of Shikhani, there was a mean follow-up of only 2.8 mean number of person-years, which probably accounts for the zero percentage incidence after 5 years (14). There was a statistically significant difference in the cumulative incidence in the global population with an index tumour in the head and neck region versus the laryngeal index tumour site population and this was true for the cumulative incidence after 1 year (p=0.008) and after 2 years (p=0.001) as assessed by a Mann-Whitney U-test (Table 9).

In general we can say that about half of the second primaries appear within 2 years after the detection of the index tumour but in laryngeal cancer they tend to appear

Table 9 : Meta-Analysis : cumulative incidence of second primary tumours in the overall head and neck population and in the laryngeal index tumour population.

time interval	incidence (global)	incidence index tumour larynx	
< 1 year	44.74%	21.74%	p = 0.009
< 2 years	59.65%	29.76%	p = 0.002
> 5 years	22.81%	38.10%	p = 0.40

(Mann-Whitney U-test)

somewhat later in the course of follow-up. In both groups they continue to occur even 5 or more years after the appearance of the index tumour.

The risk for second cancer is, in some studies, expressed by annual incidence, which is interesting given the varying follow-up of the different studies included in the meta-analysis. Tepperman et al. reported a constant rate of development of second primary cancers after oral cancer of 3.6% per year for at least the first 10 years of follow-up (15). Wagenfeld et al calculated the rate of development of the second respiratory tract tumour after glottic carcinoma, which was 1.3% per year and constant with time. No difference was observed between different stages of disease (16). For supraglottic carcinoma, a rate of almost 4% per year was reported (17).

4. Influence of the second primary tumour on survival

Finally we looked at the outcome of the patient, once a second primary tumour had been diagnosed. Unfortunately, the data of the different studies were unfit for statistical analysis.

CONCLUSION

Multiple primary tumours are an important phenomenon in head and neck cancer. They are partially responsible for the fact that although treatment protocols have significantly improved the local and regional control of head and neck cancer, the gain in survival remains relatively modest. In general we can say that once a second tumour is diagnosed the outcome is poor for most patients. The reasons for this are multiple. Firstly there is a high incidence of lung and oesophageal cancer, both of which have a poor prognosis (15). Secondly, the second primary tumour is often in an advanced stage, and at last these second, and sometimes multiple cancers, when appearing in the head and neck area, are frequently resistant to further therapy

because they often occur in a previously treated field, defying effective treatment (16,17). If we want to improve the long-term survival of these patients, we must address this phenomenon of multicentricity of squamous cell carcinoma. Primary prevention of the development of a second cancer is a desirable objective. Although supporting data were not available in this study, other studies have shown that patients who continue to smoke are at particularly high risk of second primaries as compared to those who stop smoking (18,19,20). But anti-smoking efforts are, at best, only sporadically successful. Furthermore, the occurrence of a second cancer early in follow-up suggests that the smoking and drinking habits of most patients prior to the appearance of the index tumour play a primary role in further tumour occurrence. After quitting smoking, the chance of developing a second primary cancer only gradually decreases over the course of years. The mucosa has been primed and retains a malignant potential (14). An alternate method of prevention would be the use of a medication which would prevent the malignant transformation in the mucosa. Much work is currently being done to estimate the value of chemoprevention using synthetic vitamin A derivatives and N-Acetyl cysteine, but this is still an object of clinical research (21,22,23,24). The best method of improving the survival in cases of multiple primary cancers seems to be early detection so that they can be treated in an early stage with, hopefully, an increase of the survival rate. Several reports have recommended a more systematic search for additional primary lesions in all patients with newly diagnosed head and neck malignancies and have advocated a more thorough follow-up of those patients (17,25,26,27). We can state that the physician engaged in the care of patients with cancer of the head and neck should be familiar with the concept of multicentricity. Careful vigilance should be exercised during the initial work-up and the follow-up period, not only looking for recurrences of the original lesion, but also to actively identify further primary cancers as early as possible. At this stage, it is not clear whether screening of head and neck cancer patients will improve mortality rates, and even less clear whether they are cost-effective. Some authors state that each follow-up examination can not be limited to the upper aero-digestive tract. The medical oncology literature supports their findings that bladder, prostate, colon, and digestive tract tumours (stomach, pancreas) are significantly higher in patients with aerodigestive tract tumours. Complete follow-up of the head and neck tumour patient should therefore ideally include annual evaluation of the urologic and gastrointestinal systems (12).

Understanding the molecular events underlying the development of second primary malignancies may help develop stategies for the prevention and therapy of these cancers.

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CHAPTER 3

CLINICAL CHARACTERISTICS AND DIAGNOSTIC DELAY OF HEAD AND NECK CANCER: RESULTS FROM A PROSPECTIVE STUDY IN BELGIUM.

Clinical characteristics and diagnostic delay of head and neck cancer: results from a prospective study in Belgium.
I J Dhooge, FWJ Albers, PB Van Cauwenberge
Eur J Surg Oncol 1996; 22

ABSTRACT

A prospective study of head and neck cancer patients was started to gather information about topographic and clinical characteristics of head and neck cancer, alcohol and nicotine use and the delay in diagnosis. More than half of the patients consulted our institution with an advanced stage of disease. As was expected, we found a positive association between the size of the tumour and the clinical stage of the neck. Concerning nicotine and alcohol use, our results support the hypothesis that tobacco smoking is more strongly associated with lesions in sites heavily exposed to inhaled smoke, whereas alcohol consumption has a stronger effect on structures belonging to the «food channel» and reservoir systems. We found no association between delay and tumour stage at diagnosis, but a statistical significant correlation was found between the delay and the tumour site. This leads us to conclude that the tumour stage at diagnosis is determined mostly by the biology of the tumour.

INTRODUCTION

Treatment protocols of head and neck cancer patients have improved considerably over the last 50 years. Advances in reconstructive surgery, combined with radiotherapy, and eventually chemotherapy, have improved local and regional tumour control. Unfortunately, there is only a modest impact on survival. Loco-regional recurrence is still the major cause of death, but the occurrence of new tumours in the same patient, and the development of distant metastases also may jeopardize the survival of head and neck cancer patients. Therefore, we have to look for different ways to improve the outcome of a head and neck cancer patient. A better insight in the relationship between nicotine and alcohol use and the localization of the head and neck tumour could help us in defining a subpopulation more at risk. Secondly, campaigns for early diagnosis are advocated by some investigators because, theoretically, delayed diagnosis should inevitably be associated with advanced disease. But it is important to know if there is indeed a correlation between the delay in diagnosis and the tumour stage of disease. Therefore, we started a prospective study in October 1990 at the Department of Otorhinolaryngology of the University Hospital of Ghent (Belgium) in head and neck cancer patients to gather information about topographic and clinical characteristics of head and neck cancer, alcohol and nicotine use and the delay in diagnosis.

PATIENTS AND METHODS

In a 24-month period, we collected data of 127 consecutive patients, referred to the Department of Otorhinolaryngology of the University Hospital of Ghent (Belgium) with previously untreated, squamous cell carcinoma (SCC) of the head and neck region. Patients with a malignancy of the skin, the paranasal sinuses, nasopharynx, salivary glands or thyroid were excluded. We used standardized forms to gain information about tobacco and alcohol use at the time of diagnosis, the medical history concerning previous malignancies and the delay in referral. The use of tobacco was expressed in pack year (one pack year = equivalent of smoking one package of cigarettes per day during one year) and we made a difference between the smokers of filter cigarettes, non-filter cigarettes, pipes and cigars. One cigar and one pipeful were assumed to be equal to respectively 4 and 2 cigarette equivalents. The intake of alcohol was expressed in units of alcohol per day, assuming that the amount of alcohol in a consumption of hard liquor, wine and beer is equal (approximately 10 g of alcohol per unit). Drinkers of alcohol were divided into 6 groups according to the number of units they drank per day.

The site and subsites of the head and neck were defined according to the criteria of the International Union Against Cancer (UICC) and the International Classification of Diseases for Oncology (ICD-O) (1). In case a tumour involved more than one (sub)site, we chose the (sub)site in which the bulk of the tumour was localized. Regarding the tumour size and lymph node involvement, all tumours were coded according to the latest UICC TNM classification (1). Lymph node involvement was decided on clinical examination and the results of the CT scanning. Fine-needle aspiration biopsy was routinely done to confirm metastatic lymph node cancer.

STATISTICS

Comparison of the different sites was performed using non- parametric tests. For qualitative variables such as tumour stage and categories for smoking habits and alcohol intake, the chi-square test has been used. For continuous variables we used the Kruskal-Wallis and Mann-Whitney U-test. The correlation between delay and tumour stage, and tumour stage and clinical stage of the neck, has been expressed using the Spearman correlation coefficient (rS).

To evaluate the role of alcohol and smoking as possible determinants of SCC in the various head and neck sites, a case-case study has been performed. As no reference group of persons without SCC was available as in a case-referent design, relative risks (RRs) for SCC at these sites could not be directly estimated. However, the odds ratios (ORs) for the association between the different sites of the tumour and the alcohol and nicotine abuse could be estimated. These ORs can be equated with ratios of RRs. Patients with SCC of the larynx, being the largest subgroup, have been used as the reference group.

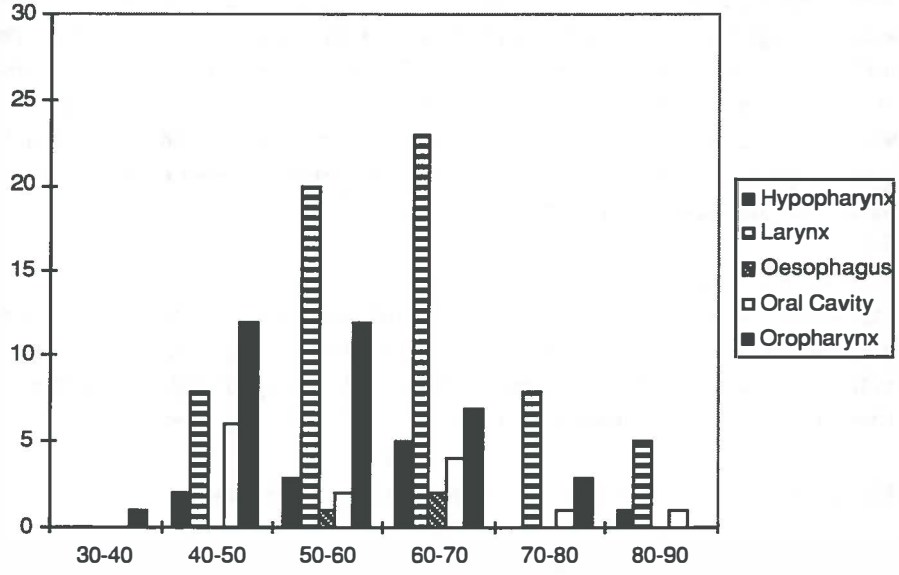
By use of the Mantel-Haenszel method (X2-test for stratified 2x2 contingency tables) the OR associated with the use of tobacco and alcohol were adjusted for possible confounding by each other. Dose-response relationships were assessed to be the stratified test for linear trend. As we had no reference population of non-users, moderate and heavy users of tobacco (< 30 pack year versus > 30 pack year) and alcohol (< 5 units/day versus > 5 units / day) were contrasted with each other. The possibility of a different synergistic effect of the use of tobacco and alcohol and the anatomical sites head and neck SCC was explored by likelihood ratio tests of uniformity of the OR.

RESULTS

1. Age and gender distribution

The group of 127 patients with SCC of the head and neck region consisted of 116 men and 11 women (male to female ratio : 10 to 1). The mean age and the median for men and for women were 59 and 58 years respectively. The age distribution for the different sites is shown in Figure 1. The median age for the different sites is 62 years for laryngeal carcinoma, 54 years for oropharyngeal carcinoma, 58 years for carcinoma of the oral cavity, 61 years for hypopharyngeal carcinoma and 64 years for oesophageal carcinoma.

Fig. 1 : Age distribution for the different sites



2. Site and stage distribution

The location and stage distribution of the different index tumours is given in Table 1. Half of the patients had laryngeal cancer : 26 glottic carcinomas, 18 supraglottic carcinomas, 18 transglottic carcinomas and two subglottic carcinomas.

Site and T and N

When looking at the tumour size, it appears that SCC of the hypopharynx is diagnosed significantly more often in an advanced stage (T3-T4) than in other subsites ($P<0.001$ Mann-Whitney U-test). We also found a statistically significant difference in tumour size between tumours of the oropharyngeal region and tumours of the larynx, tumours of the oropharynx being diagnosed more often in an advanced

Table 1 : The site and stage distribution of the index primaries of 127 patients.

Index primary site	No	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
oral cavity	14	-	-	4	4	6
oropharynx	35	2	7	5	12	9
hypopharynx	11	1	1	4	2	3
larynx	64	-	7	17	15	25
oesophagus	3	-	-	-	-	3
Total	127	3	15	30	33	46

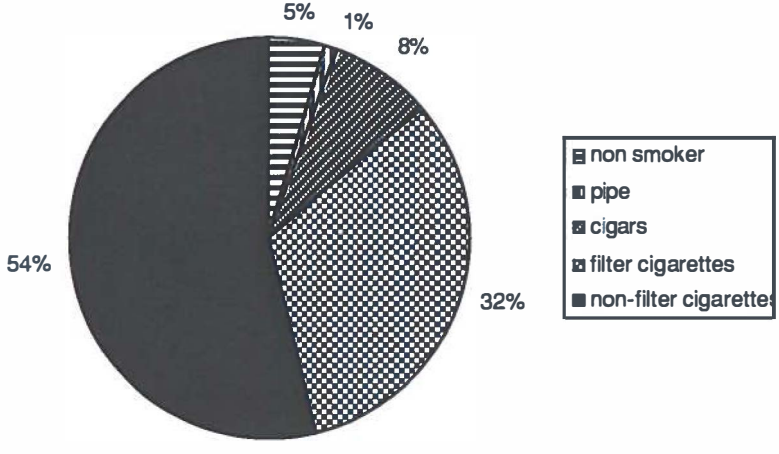
No : number of patients

stage of disease (T3-T4) than laryngeal cancer (P=0.004 Mann-Whitney U-test). When looking at the clinical stage of the neck (N), we found a highly significant statistical difference between the stage of the neck in laryngeal carcinoma compared with the neck stage in the other sites (p=0.007 Mann-Whitney U-test). The majority of the laryngeal carcinomas had no pathological lymph nodes. We found a positive association between the size of the tumour (T) and the clinical stage of node involvement (N) ($rS = 0.204$, $p = 0.025$ Spearman correlation coefficient). The larger the tumour, the more advanced the stage of the neck.

3. Tobacco and alcohol

The distribution of the smoking habits of the patients is shown in figure 2. Smoking of cigarettes is by far the most common way to use tobacco (86%) and more than half of the male population use non-filter cigarettes. Other tobacco habits like sniffing or chewing tobacco are uncommon in Belgium.

Fig. 2 : Distribution of smoking habits of 127 head and neck cancer patients



The distribution of the pack-years shows that the majority of the head and neck cancer population, men as well as women, are heavy abusers of nicotine (Fig 3). The distribution of alcohol intake for the whole population is shown in Figure 4. About half of the patients drink more than 5 units of alcohol per day. There is no proven statistical difference in the smoking habits for the different sites (p=0.43 Chi-square). There is, however, a strong statistical significant difference between the different sites according to their alcohol use (p = 0.0052 Chi-square). The highest alcohol abuse was found in the group of oral cavity and oropharyngeal cancer comparrd with the group of patients with laryngeal and hypopharyngeal cancer. We could not demonstrate a linear relation between tobacco and alcohol use. Heavy smokers are not necessarily heavy abusers of alcohol (p=0.25 Chi-square).

Fig. 3 : Distribution of pack years of 127 head an neck cancer patients

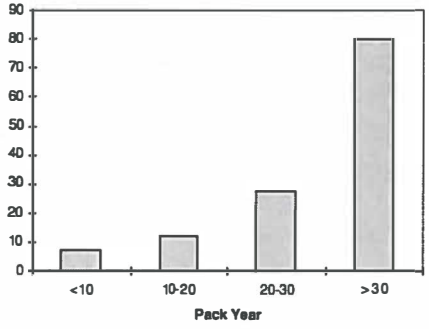
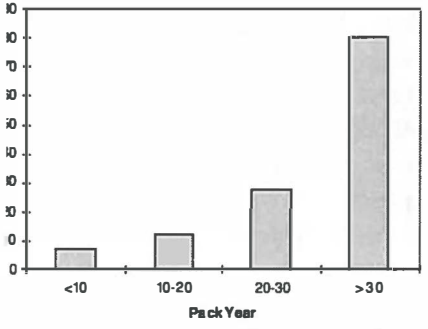


Fig. 4 : Distribution of alcohol instake in 127 head an neck cancer patients



The ORs for the sites of head and neck related to the use of tobacco and adjusted for alcohol are presented in Table 2. The highest ORs were seen in the oral cavity and the oropharynx (1.99 and 1.76 for heavy smokers in comparison to moderate smokers). The lowest ORs were seen in SCC of the hypopharynx.
The ORs for the different sites related to the use of alcohol and adjusted for nicotine are given in Table 3. SCC of the oropharynx is significantly more associated with the use of alcohol than laryngeal cancer. A high OR was also seen in oral cavity cancer.

Table 2 : Dose-specific odds ratios (ORs) for the use of tobacco, adjusted for the use of alcohol, of squamous cell carcinoma of the head and neck related to the different sites, using laryngeal cancer patients as a reference group.

Sites	OR	95% CI	p
Oralcavity	1.99	0.31<1.99<15.97	0.68
Oropharynx	1.76	0.45<1.76< 7.43	0.54
Larynx	1	-	-
Hypopharynx	0.51	0.10<0.51< 2.55	0.57

CI : confidence interval

Table 3 : Dose specific odds ratios (ORs) for the use of alcohol, adjusted for the use of tobacco, of squamous cell carcinoma of the head and neck related to the different sites, using laryngeal cancer patients as a reference group.

Sites	OR	95% CI	p
Oropharynx	5.64	1.66<5.64<20.06	0.004
Hypopharynx	2.8		
Oralcavity	2.71	0.55<2.71<13.93	0.30
Larynx	1	-	-

CI : confidence interval

4. Delay in diagnosis of squamous cell carcinoma of the upper respiratory tract

The referral pattern of our population under study is given in Table 4. Almost two-thirds of our study population was referred to the university by ENT surgeons working in private practices. Very few patients consulted directly without any referral. Patients' delay was defined as the period of time between the point of noticing a discomfort and the time of biopsy-proven diagnosis. The delay has been related to patient variables such as gender, tumour stage and tumour site. The delay for both sexes is given in Table 5. In about half of the male patients and three-quarters of the female patients the diagnosis is made within three months of the beginning of the complaints.

Table 4 : Referral pattern of 127 head and neck cancer patients.

ENT- surgeon	69
Generalpractitioner	39
noreferral	7
Maxillo-facialsurgeon	5
Internalmedicine	4
Neuro-surgeon	2
Dermatologist	1
Total	127

Table 5 : Delay in diagnosis of 126 patients with head and neck cancer related to gender.

Delay	males (%)	females
nocomplaints	6 (5.2%)	0
0-3 months	62 (53.4%)	8
4-6 months	21 (18.1%)	1
7-12 months	9 (7.7%)	0
> 12 months	18 (15.5%)	2
Total	116	11

Delay - Tumour stage.

There is no significant correlation between the tumour stage and the overall delay (rS = 0.090, p = 0.33 Spearman correlation coefficient).

Delay - Tumour site

There is a statistically significant difference between the different sites for the overall

delay (p = 0.013 Kruskal-Wallis 1-Way ANOVA). The delay in diagnosis of the patients with a tumour in the oropharyngeal region is shorter than the delay in laryngeal cancer patients (p = 0.0017 Mann-Whitney U-test).

DISCUSSION

More than half of the patients consulted our institution with an advanced stage of disease (stage III or IV). Treatment of head and neck cancer in Belgium is not restricted to specialized centres. Small cancers are often treated in a private ENT practice. This biases the cancer population we see at the university hospital.

As expected, we found a positive association between the size of the tumour and the clinical stage of the neck. There was, however, a statistical significant difference between the stage of the neck in laryngeal cancer and the neck stage in the other sites. The majority of the laryngeal cancer patients had no pathological lymph nodes. A possible explanation is that firstly, laryngeal cancer, in comparison with oropharyngeal and hypopharyngeal cancer, was more often diagnosed in an earlier tumour stage (T). Secondly, for glottic and subglottic carcinoma, lymphogenic spread occurs rather late in the course of the disease.

The tumour size of a hypopharyngeal carcinoma at diagnosis was significantly larger compared to the other sites. This is probably due to two factors: the early symptoms of hypopharyngeal carcinoma are often aspecific; so the pre-clinical phase is long. Secondly, the clinical examination of the hypopharynx is difficult.

Tobacco and alcohol are considered the most important aetiological factors in the development of squamous cell carcinoma (SCC) of the head and neck region (2,3,4,5,6,7,8). Other factors such as occupational or environmental factors, genetic or nutritional elements do not have the same importance (9,10). As both, tobacco and alcohol, are important aetiologic factors in the development of head and neck cancer, it is necessary when analysing one of the factors to control for the other. This present study suggests, that the RR for users of tobacco and alcohol to develop SCC of the head and neck, varies by anatomical site. The estimated OR of 1.99 for heavy smokers with SCC of the oral cavity (relative to SCC of the larynx and compared with moderate smokers) means that for heavy smokers the RR for the development of SCC of the oral cavity is about twice as high as the RR for SCC of the larynx, which is about twice as high again (1 : 0.51) as the RR for SCC of the hypopharynx. For alcohol, however, we see that for heavy drinkers the RR for the development of SCC of the oropharynx is about 5.6 times higher than the RR for SCC of the larynx, which is highly statistically significant. These results support the hypothesis that tobacco smoking is more strongly associated with lesions on sites heavily exposed to inhaled

smoke, whereas alcohol consumption has a stronger effect on structures belonging to the «food channel» and reservoir systems (11,12,13). Many studies have shown that there is a strong dose-risk relationship for nicotine as well as for alcohol and cancer of the upper aerodigestive tract (14). Until now, studies examining the joint effect of alcohol and tobacco cannot conclude if the interaction is better described by an additive or multiplicative model.

Concerning the delay, we do not know from this study if the overall delay consist primarily of patients' delay (= the time period between the start of the complaints and the first visit to a doctor) or of doctors' delay (= the time period from the first consultation until the final diagnosis). The absence of a significant association between the overall delay in diagnosis and tumour stage is in agreement with the finding in the literature (15,16,17,18,19,20). Only Mashberg et al. found that patients with T1 cancers had a shorter overall delay than patients with larger lesions (21). The lack of association between delay and tumour stage at diagnosis suggests that the tumour stage at diagnosis is determined by the intrinsic difference in tumour aggressiveness (17). A statistically significant correlation was found between the delay and the tumour site. The overall delay in diagnosis of laryngeal cancer is longer than oropharyngeal tumours. This reflects the specific anatomical differences between the different sites. A tumour developing in the larynx gives rise very early to minor symptoms like hoarseness. But, in contrast to what we generally believed, dysphonia is apparently not considered an alarm symptom. Oropharyngeal tumours, when becoming clinical, give rise to serious complaints such as dysphagia, odynophagia and otalgia urging the patient to seek medical attention. This finding was confirmed by others (19,22). We can conclude that the tumour stage at diagnosis is determined mostly by the biology of the tumour and not so much by the delay in diagnosis. The delay reflects the clinical phase of the tumour which varies from site to site rather than it reflects the behaviour of the patient.

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CHAPTER 4

PANENDOSCOPY AS A SCREENING PROCEDURE FOR SIMULTANEOUS PRIMARY TUMOURS IN HEAD AND NECK CANCER

Panendoscopy as a screening procedure for simultaneous primary tumours in head and neck cancer.
IJ Dhooge, M De Vos, FWJ Albers, PB Van Cauwenberge
Eur Arch Otorhinolaryngol 1996; in press

ABSTRACT

Head and neck cancer is often associated with second primary neoplasms. These cancers most commonly involve other regions of the head and neck, esophagus, and lung. The majority of cases are also squamous cell carcinomas. In view of this rather frequent occurrence of multiple primary cancers and how they adversely affect the patient's survival, it becomes imperative to analyze how the clinician can intervene effectively. One such approach is to detect multiple primaries as early as possible.
As such, panendoscopy as a part of the tumour-staging procedure has been advocated by many investigators to search for simultaneous second primary malignant neoplasms in patients presenting with head and neck cancer. In a 24-month period, data were gathered from 127 consecutive patients referred to University Hospital, Ghent with previously untreated, squamous cell carcinomas of the head and neck. One hundred-eighteen patients underwent an endoscopic examination under general anesthesia, during which 4 simultaneous second primary tumours were found in 3 patients. This represents an incidence of 3.4% of simultaneous second primary neoplasms. The results for the different parts of the endoscopy are discussed and compared with literature findings. Guidelines are given for the initial evaluation of the head and neck cancer patient.

INTRODUCTION

Head and neck cancer is often associated with second primary neoplasms. These cancers most commonly involve other regions of the head and neck, esophagus, and lung. The majority of cases are also squamous cell carcinomas. When these tumours occur at the same time, they are called simultaneous primary tumours.
Most early reports on multiple primary cancers of head and neck were retrospective studies reporting incidences varying from 3% to 30%, with an average of 5%. Later, prospective studies were started that performed routine panendoscopic examinations of the upper aerodigestive tract. Incidences of simultaneous primary cancer were reported to vary from 10% to 16% (4,15,31,43). However, geographic and racial differences were found in the occurrence of simultaneous primary tumours. In The Netherlands, for instance, incidences of 1.5% were reported (19). As a consequence, there still is some controversy about the need to perform a panendoscopic procedure in every patient with an index tumour in the head and neck area. In the present study, we performed a prospective panendoscopic evaluation of patients presenting with a new, untreated cancer of the head and neck. The goals of our study were to determine the regional incidence of simultaneous primary tumours of the head and neck in this population; determine the value of bronchoscopy and bronchial washings in the presence of normal chest radiographs; determine the value of rigid esophagoscopy for detection of simultaneous esophageal cancer and to investigate the potential morbidity of the panendoscopic procedure.

PATIENTS AND METHODS

From October 1990 to October 1992, we collected data from 127 consecutive patients referred to the Department of Otorhinolaryngology, University Hospital, Ghent (Belgium). All had previously untreated, squamous cell carcinomas of the head and neck. Patients with a malignancy of the skin, paranasal sinuses, nasopharynx, salivary glands or thyroid were excluded.
Preoperatively, a thorough clinical examination was done that included indirect laryngoscopy and chest roentgenography. CT scans from the skull base to the clavicles were obtained in every patient. Routine contrast studies of the gastrointestinal system were not performed unless symptoms of dysphagia were indicated by history. The patients underwent a panendoscopic examination under general anesthesia as part of the initial staging procedure of their presenting tumour. After induction, patients were ventilated using high-frequency jet ventilation. Bronchoscopy with a rigid bronchoscope and rigid endoscopes (0°, 30°, 90° and 120°) was performed first. Selective bronchial washings for cytological evaluation were obtained regardless of the endobronchial findings. Then rigid esophagoscopy

with 0° and 30° endoscopes was performed. A Jako or Dedo type wide-lumen laryngoscope was used to view the larynx, pyriform sinuses and hypopharynx. The examination was concluded with final inspection and palpation of the oral cavity and oropharynx. Nasopharyngoscopy was performed with a Wolf Lumina nasopharyngoscope.

Warren and Gates' (42) criteria were used to define a second primary tumour. The original presenting tumour was termed the index tumour. The site and subsites of the head and neck were defined according to the criteria of the International Union Against Cancer (UICC) and the International Classification of Diseases for Oncology (ICD-O). If a tumour involved more than one (sub)site, we chose the (sub)site in which the bulk of the tumour was localized.

Regarding tumour size and lymph node involvement, all tumours were coded according to the latest UICC TNM classification (18). Lymph node involvement was determined by clinical examination together with the results of CT. Fine-needle aspiration biopsy was done routinely to confirm metastatic lymph node cancer.

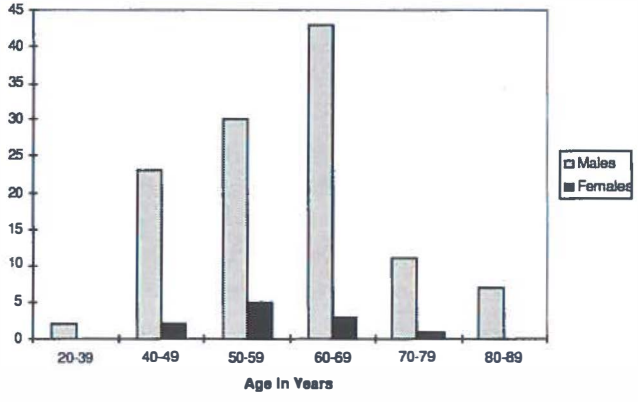
Simultaneously developing carcinomas were categorized as lesions that developed at the same time and were diagnosed at the initial presentation. These are considered to be a subclass of synchronous primary malignant tumours that aree defined as separate cancers which were diagnosed within 6 months of one another.

RESULTS

1. Age and gender distribution

The group of 127 patients with squamous cell carcinoma of the head and neck region consisted of 116 men and 11 women (male to female ratio : 10 to 1). The mean ages

Fig. 1 Distribution of 127 patients with cancer of the upper aerodigestive tract by gender and age



for the men and women were, respectively, 59 and 58 years. The sex and age distribution is shown in Fig. 1.
In about half of the male patients and three-fourths of the female patients the diagnosis was made within 3 months after the onset of complaints.

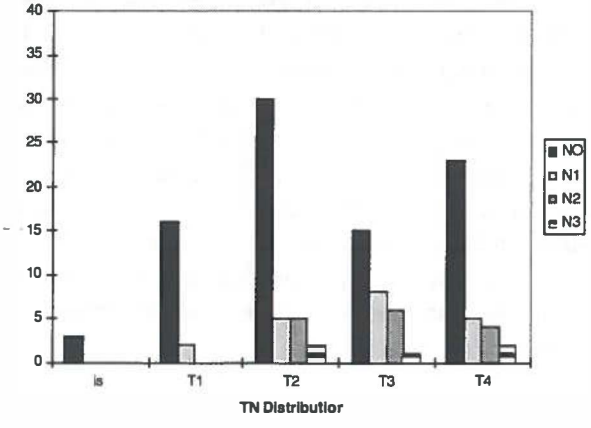
2. Site and stage distribution
The site and stage distribution of the different index tumours is given in Table 1.

Table 1 The site and stage distribution of the index primaries of 127 patients managed at University Hospital, Ghent

Index primary site	No	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Oral cavity	14	-	-	4	4	6
Oropharynx	35	2	7	5	12	9
Hypopharynx	11	1	1	4	2	3
Larynx	64	-	7	17	15	25
Esophagus	3	-	-	-	-	3
Total	127	3	15	30	33	46

Sixty-four patients had laryngeal cancer : 26 glottic carcinomas, 18 supraglottic carcinomas, 18 transglottic carcinomas and 2 subglottic carcinomas. There was no statistically significant difference between the stage distribution of the different tumour sites. Fig 2 shows the distribution of the patients with head and neck carcinoma by tumour stage and lymph node involvement.

Fig. 2 Distribution of 127 patients by tumour stage (T) and lymph node (N) involvement



3. Findings of the panendoscopic procedure

A full endoscopic procedure was performed in 91 of the 127 patients. In 27 of the patients bronchoscopy and bronchial washings were not done because of severely impaired respiratory function. In 9 patients, only an examination of the oral cavity and oropharynx was done because of anatomical deformities or large tumours prohibiting endoscopy.

Four of the 91 patients who underwent the full endoscopic procedure had a complication (4.5%). One loose tooth occured in one patient. In 2 patients a tracheotomy had to be performed during the examination because in both cases tumour was so bulky that detubation was considered unsafe for maintenance of an airway. One patient remained intubated for 2 days after the procedure because of the same reason. There were no deaths or major complications (such as perforation of the esophagus) in the patients studied.

In the group of 118 patients undergoing endoscopy, 4 simultaneous second primary tumours were found in 3 male patients at the time of endoscopy (Table 2). In all, this represented an incidence of 3.4% of simultaneous second primary tumours.

Table 2 Patients with simultaneous primary tumours

Age	Locationls primary tumor	T-class of li primary tumour	Location 2nd primar tumour	T- class of 2nd primar tumour	Location 3rd primary tumour	T- class of 3rd primary tumour	Part of endosco leadingto diagnosis	Survival (month
64	esophagus	T4N0M0	lung	T2	-	-	Bronchialwashing	3
57	oropharynx	T4N3M0	larynx	T2	-	-	Laryngoscopy	10
42	nropharynx	T3N0M0	hypopharynx	T2	larynx	T2	Laryngo- hypo-oropharyngo-scopy	4

Bronchoscopy and bronchial washings

Ninety-one patients underwent rigid bronchoscopy and had bronchial washings collected during bronchoscopy. Bilateral positive bronchial washings with a normal chest radiograph were considered to represent contamination. Only unilateral positive bronchial washings were considered to be significant and CT of the chest was performed. In one patient a lung tumour was found. This patient had a bronchial washing positive for a malignant neoplasm, but no evidence of tumour was found on chest roentgenograms or bronchoscopy. The diagnosis was confirmed by CT of the chest and flexible bronchoscopy with broncho- alveolar lavage. As the histology of the lung tumour (oat cell) was different from that of the head and neck tumour (which was a squamous cell carcinoma) there was no difficulty in fulfilling the criteria of Warren and Gates. The site of the primary lesion in this patient was a large cervical esophageal carcinoma. There were no cases in which radiography was positive and bronchoscopy was negative.

Esophagoscopy
One hundred-eighteen esophagoscopies were performed. No second primary in the esophagus was found.

Direct pharyngoscopy and laryngoscopy
One hundred-eighteen patients underwent oro- hypopharyngoscopy and laryngoscopy. Two second simultaneous primary tumours were found and a third simultaneous primary tumour. Two tumours were supraglottic laryngeal carcinomas and one was a hypopharyngeal (pyriform sinus) carcinoma. The primary carcinomas in both patients were large (T3-T4) tonsillar carcinomas that made difficult thorough initial examination of the hypopharynx and larynx and prevented their diagnosis prior to endoscopy. All three second primary lesions were T2 lesions.

DISCUSSION

The reported incidence of 3.4% of simultaneous primary tumours in the aerodigestive tract is consistent with findings reported from the Netherlands (19) but is low compared to other series deriving mostly from studies in the United States (Table 3). The reasons for this discrepancy are multiple. In a number of American studies, a hospital or regional tumour registry is used for the collection of the data, which explains the large proportion of second tumours found outside the aerodigestive system. In our study, however, the prevalence data are the result of an intensive clinical surveillance of ENT doctors and are therefore mainly restricted to the head and neck area. Secondly, racial, environmental and occupational factors are of importance in the development of head and neck carcinoma. Other studies stress the importance of vitamin A and E as protective factors against the development of head and neck cancer in general and in second primary tumours in particular (11). Thus nutritional habits of a population are important. The prevalence of multiple primary tumours also depends on the site of the index tumour. Since a lot of these parameters are not mentioned in the different studies, it is difficult to compare different studies with each other.

Chest radiography versus bronchoscopy
There is no clinical consensus regarding the use of either rigid or flexible bronchoscopy to evaluate patients with primary squamous cell carcinomas of the upper aerodigestive tract for the possibility of second primary cancers. Whereas its effectiveness in patients with questionable lesions or masses on chest radiographs is certain, the value of this procedure in a patient with a normal chest radiograph remains questionable.

Table 3 Incidence of simultaneous second primary carcinomas of the esophagus, lung and head and neck region in patients with a primary head and neck carcinoma (pr prospective, re retrospective)

Authors (reference)		n	No tumour head and neck	%	No esophag tumour	%	No lung tumour	%
McGuirt (32)	pr	100	6	6%	8	8%	3	3.0%
Maisel (31)	pr	449	12	2.7%	4	0.9%	17	3.8%
Weaver (43)	pr	124	11	8.9%	3	2.4%	2	1.6%
Atkins (3)	pr	451	5	1.1%	3	0.7%	3	0.7%
Leipzig (29)	pr	384	14	3.6%	7	1.8%	13	3.3%
Parker (33)	pr	208	10	4.8%	4	1.9%	3	1.4%
Lau (27)	pr	105	5	4.8%	6	5.7%	1	1.0%
Gluckman (15)	pr	162	12	7.4%	2	1.2%	1	0.6%
Grossman (16)	re	696	25	3.6%	6	0.9%	7	1.0%
Schuller (35)	pr	53	3	5.7%	0	0%	2	3.7%
Hordijk (19)	pr	100	1	1%	0	0%	1	1%
Atkinson (4)	pr	271	13	4.5%	12	4.4%	3	1.1%
Choy (8)	pr	573	1	0.2%	8	1.4%	1	0.2%
Present series	pr	118	3	2.4%	0	0%	1	0.8%
Shapsay (36)	pr	150	-	-	9	6%	-	-
Abemayor (1)	pr	150	-	-	3	2%	-	-
Grossman (16)	pr	254	-	-	4	1.6%	-	-

n : number of patients with Head and Neck cancer
No : number of patients with simultaneous primary cancer

The incidence of a second synchronous primary cancer in the lung varies from 0.2% to 3.8% (Table 3). Table 4 gives the yield of bronchoscopy in detecting simultaneous primary lung tumours in patients with a normal chest radiograph. The chest roentgenogram is not an absolute indicator of the presence of second primary lesions in the lung. But because of the very low yield, an argument can be made against including rigid bronchoscopy as part of the panendoscopic evaluation when the chest roentgenogram is normal.

Table 4 Yield of bronchoscopy in detecting simultaneous primary lung tumours in patients with normal chest radiographs (n number of patients with head and neck cancer)

Author (Reference)	n	No	No'	No'/No
Leipzig(28)	98	3%	3%	100%
Vrabec (41)	1518	0.6%	0.3%	50%
McGuirt (32)	100	3%	1%	33%
Maisel (31)	449	3.8%	0%	0%
Parker (33)	208	1.4%	0.5%	36%
Present series	127	0.8%	0.8%	100%

No : number of patients with simultaneous primary lung carcinoma
No' : number of patients with simultaneous primary lung carcinoma detected only by either rigid or flexible bronchoscopy
No'/No : percentage of the total number of patients with simultaneous primary lung carcinomas detected only by bronchoscopy

In general, the sensitivity of rigid bronchoscopy is rather low (10,27). Examination using a fiberoptic endoscope is increasing in popularity. The flexible instrument is not as traumatic as the rigid instrument because of its flexible shaft and its smaller caliber. Examination of the lungs can be performed more thoroughly and segmental bronchial washings can readily be obtained (9,14,21,354). Conventional white light bronchoscopy , however, fails to detect precancerous or early lung lesions in about 10-20% of cases. A report by Woolner and colleagues (44) showed that even for centrally located squamous cell carcinomas, carcinoma in situ was visible to the experienced bronchoscopist in only 29% of cases.
Fluorescence bronchoscopy has been developed over the last two decades to address the limitations of conventional techniques (5,17). This type of bronchoscopy uses fluorescing drugs that are preferentially retained in tumours. However, their diagnostic effectiveness has been limited because these tumour-localizing drugs, such as Photofrin or Hematoporphyrin Derivative, have serious side effects of prolonged skin photosensitivity (12). Lam et al. (23,24) showed in experimental and clinical studies that carcinoma in situ could be detected with much lower dose of Photofrin II with no apparent skin phototoxicity. An exciting finding was their discovery that detection of dysplasia and carcinoma in situ could be achieved without using any drug at all (20,21,22,25). Using a helium-cadmium laser (442 nm) for illumination, they saw a significant decrease in autofluorescence intensity in areas with dysplasia or carcinoma in situ compared to normal bronchial tissue. Using this technique, they

were able to increase the sensitivity of the fluorescence system to 72.5% in detecting dysplasia and carcinoma in situ, which is 50% higher than that of the white light bronchoscopy (22,25). Although not available at all medical centers, this technique is an important adjunct to conventional white light examination for improving the ability to diagnose lung cancer even in a very early stage.
In our opinion, rigid bronchoscopy should not be performed routinely at the initial work-up of the head and neck cancer patient if a chest radiograph is normal. Flexible bronchoscopy with segmental bronchial washings and in some occasions using fluorescence imaging may have a higher yield, but more data are necessary before definite conclusions can be drawn. As most lung tumours occur metachronously in head and neck cancer patients, the biggest advantage will lay in the course of follow-up.

The role of esophagoscopy in the initial work-up
The incidence of simultaneous primary esophageal tumours is relatively low in a Western population. In our study, no simultaneous primary tumours of the esophagus were detected. Most authors report an incidence of 1-2%, although some studies have found incidences as high as 6-8% (Table 3). Studies reporting the results in a Chinese or Japanese population note a definite higher incidence of second primary esophageal cancer (26). Considering the overall number of simultaneous asymptomatic esophageal malignancies, incidences are still lower (Table 5). This explains the divergence of opinion among otolaryngologists on the value of esophagoscopy as a routine screening procedure at the initial evaluation of a head and neck cancer patient. Further, survival after diagnosis of any primary esophageal cancer has been poor

Table 5 Incidence of simultaneous oesophageal malignancies

Author	n	No	No'	No'/No
McGuirt (32)	100	8 %	3.7%	46%
Atkinson (4)	271	4.4%	1.1%	25%
Shapsay (36)	150	6 %	2.7%	45%
Choy (8)	573	1.4%	0.9%	64%
Atabek (2)	574	1 %	0.2%	20%
Present series	127	0 %	0 %	-

n : number of patients with head and neck cancer
No : percentage of simultaneous esophageal malignancies
No' : % of simultaneous asymptomatic esophageal malignancies, No'/No percentage asymptomatic esophageal malignancies of the total number of esophageal malignancies

(30,32). This is due to the presentation of most patients with an advanced stage of disease (29). At time of diagnosis, only 30 % of patients on average, are actually considered resectable and curable (7,38). Five-year survival rates after combination surgery and radiation therapy are generally in the range of 15-25% (13). Even worse, in a study of 153 cases of primary esophageal cancer patients reported by Takita et al (39), there was only a 2% 5-year survival rate with surgery and radiation therapy. The same poor survival was found in a prospective study reported by Shapsay's group (36). The value of screening lies in the ability to find esophageal cancers at an early, curable stage. However, to date there is no convincing evidence that esophageal screening during initial workup of head and neck cancer patients leads to diagnosing smaller tumours and better survival rates .

A last element to be considered when evaluating the value of rigid esophagoscopy is its complication rate. In our series we had no complications, but ours was a small series of patients. In the literature, the incidence of instrumental perforation varies from 0.2-0.8%, depending on the type of endoscopic procedure used (6,37,40,45). The risk of perforation with rigid or open-tube endoscopy is much greater than with flexible endoscopy. Although the incidence is low, the mortality can be as high as 16% (6).

From the various data reviewed, we cannot recommend esophagoscopy as a screening procedure in every head and neck cancer patient. On the other hand, esophagoscopy should be performed at the initial evaluation of the head and neck cancer patient with complaints of dysphagia or with symptoms not specific enough to be attributed to a head and neck tumour. Esophagoscopy is also warranted in patients with tumours that can possibly invade the esophagus as a consequence of their localisation or volume.

Value of direct laryngoscopy.

A large proportion of the simultaneous second primary cancers are located in the head and neck region, especially with an index tumour in the oral cavity, oropharynx or hypopharynx (Table 3). In our series, two of the three simultaneous second primaries were located in the oro-hypopharynx and larynx. Both were not diagnosed prior to endoscopic investigation. The reason is that it is often difficult to thoroughly examine the mucosa of the hypopharynx and especially that of the pyriform sinuses, the retrocricoid area, vallecula and posterior pharynx by indirect laryngoscopy, especially in the presence of another head and neck tumour.

Despite the low yield of second tumours, we support the use of oro-hypopharyngo-laryngoscopy as a screening procedure. All patients who present with head and neck cancer should undergo such endoscopy, not only for evaluation of the index tumour but also for evaluation of the entire mucosa of the oral cavity, oropharynx, hypopharynx and larynx.

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CHAPTER 5

VALUE OF RIGID BRONCHOSCOPY AND CYTODIAGNOSIS OF BRONCHIAL WASHINGS IN DETECTING BRONCHIAL CARCINOMA IN THE PRESENCE OF A CARCINOMA OF THE UPPER AERODIGESTIVE TRACT.

Value of rigid bronchoscopy and cytodiagnosis of bronchial washings in detecting bronchial carcinoma in the presence of a carcinoma of the upper aerodigestive tract.
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ABSTRACT

The results of 127 rigid bronchoscopies with bronchial washings in patients with a new, untreated head and neck tumour and a normal chest radiograph were analysed for their usefulness in detecting simultaneous primary lung carcinomas. All patients were followed for a minimum of 2 years or till death.

We found positive bronchial washings in 19 cases (21%). Unilateral positive bronchial washings were found in 8 patients (9%). In only one patient a simultaneous primary lung tumour was found. One patient was found to have a pulmonary metastasis. The remaining 6 patients with positive unilateral cytology (6/8) had normal chest roentgenograms and/or CT scans and did not develop a lung tumour in the course of follow-up. Of the 19 positive bronchial washings, 10 patients had a carcinoma of the larynx and two had a large hypopharyngeal carcinoma.

Contamination of bronchial washings with tumours cells from head and neck neoplasms limited seriously the usefulness of positive bronchial cytology.

The sensitivity and specificity of the rigid bronchoscopy with bronchial washing is too low to justify its cost.

INTRODUCTION

There is a high incidence of second primary neoplasms in patients with a known squamous cell carcinoma of the upper aerodigestive tract. Five to 30% of patients with a head and neck carcinoma will develop a second primary tumour, most frequently in the upper aerodigestive tract, lung and oesophagus. A small percentage of these second primary tumours are detected simultaneously, at the diagnosis of the initial head and neck tumour. From several reports we know that the incidence of simultaneous second primary carcinomas of the lung varies from 0.5 to 3.8%, and that the association is especially frequent with oral and laryngeal carcinoma (1). Therefore, during the initial work-up of a patient with head and neck cancer, many authors suggest screening with a rigid bronchoscopy with bronchial washings to detect a possible simultaneous second primary lung tumour.

When reviewing the literature concerning the usefulness of rigid bronchoscopy with cytodiagnosis of bronchial washing to detect bronchogenic carcinoma, there is a great deal of controversy. Some authors have reservations concerning the usefulness of the technique in the presence of a known primary tumour in the upper aerodigestive tract because of shedding of malignant cells of the primary head and neck tumour in the tracheobronchial tree (2). Others report only sporadic shedding of malignant cells into the tracheobronchial tree despite the use of rigid bronchoscopy (3,4).

In North America, the flexible bronchoscope is used by most otolaryngologists in contrast with most European centres, however otolaryngologists are trained in the use of the rigid bronchoscope, the flexible bronchoscope being almost exclusively the tool of the lung specialists. Therefore, the objective of the present study was to look at the value of rigid bronchoscopy and cytodiagnosis of bronchial washings in the early detection of bronchial carcinoma in patients treated for a primary squamous cell carcinoma of the upper aerodigestive tract.

METHODS AND MATERIAL

From October 1990 to October 1992, we collected data of 127 consecutive patients, referred to the Department of Otorhinolaryngology of the University Hospital of Ghent (Belgium) with a previously untreated, squamous cell carcinoma of the head and neck region. Patients with a malignancy of the skin, the paranasal sinuses, nasopharynx, salivary glands or thyroid were excluded. Patients with a pulmonary malignancy diagnosed by a radiologist on a chest radiograph, were also excluded from this series.

Preoperatively, a thorough clinical examination with indirect laryngoscopy and a chest roentgenography was done. CT scans from skull base to clavicles were taken in every patient. Each patient, regardless of the site and stage of his index tumour,

underwent a panendoscopic examination under general anaesthesia as part of the initial staging procedure of their presenting tumour. After induction, patients were ventilated using an endotracheal tube of 4 mm diameter and high frequency jet ventilation. Bronchoscopy with the use of the rigid bronchoscope and rigid endoscopes (0°,30°,90°,120°) was performed first. A rigid Jackson bronchoscope was used in all cases. The bronchoscope was passed through the larynx adjacent to the endotracheal tube. No attempt was made to wash the instrument after passing through the upper airway prior to obtain bronchial washings. Each main-stem bronchus was then irrigated with 10cc normal saline and aspirated for cytology in separate containers. The specimens were labelled and sent for cytologic evaluation. Smears were made: half of them were fixed in 96% ethanol and the other half were air dried. The fixed smears were stained by the Shorr technique. The air-dried smears were stained bij the modified May-Grunwald stain. The cytologic findings were reported in descriptive terms as (1) cell smears without evidence of inflammatory or preneoplastic or neoplastic changes; (2) smears without preneoplastic or neoplastic changes but with increase of inflammatory cells; (3) smears containing cells with some nuclear features of malignancy but not enough to be concluded as possible malignant and (4) smears with obvious atypical cells diagnosed as suggestive of malignancy. The tentative diagnosis is also suggested.
At the end of the study, all specimens were reviewed by the same cytologist. Only specimens diagnosed as class 4 were considered positive. Warren and Gates' criteria, modified by Hong, were used to define a second primary tumour (5,12). All patients were followed for a minimum of 2 years or till death occurred, in order to determine whether a bronchogenic carcinoma had been present which was not detected by the bronchial washing.

RESULTS

We performed a full endoscopic procedure in 91 of the 127 patients. In 36 of these patients, bronchoscopy and bronchial washings were not done because of severely impaired respiratory function, or were not possible technically because of large tumours in the upper aerodigestive tract prohibiting endoscopy.
The bronchial washings were positive in 19 cases (21%). However, bilateral positive bronchial washings with a normal chest X-ray film were considered as contamination, and no further investigations were done. In 8 cases (9%), we found an unilateral positive bronchial washing (Table 1). In those patients, the radiograph of the chest was reevaluated, and if necessary, a CT scan of the chest was performed. A lung tumour was found in one patient. This patient had a bronchial washing that was positive for a malignant neoplasm, but no evidence of tumour on chest

roentgenograms or bronchoscopy. The diagnosis was confirmed by a CT scan of the chest. As the histology of the lung tumour (oat cell) was different from that of the head and neck tumour (squamous cell carcinoma) there was no difficulty in fulfilling the criteria of Warren and Gates. The site of the primary lesion in this patient was a large cervical esophagial carcinoma. One patient with a large oropharyngeal carcinoma presented with a pulmonary metastasis at the time of diagnosis. He had a positive bronchial washing and an abnormal CT scan. He committed suicide 16 days after diagnosis. The remaining 6 patients with positive cytology (6/8) had normal chest roentgenograms and/or CT scans, four of whom were still alive at the end of the study without any signs of a lung carcinoma (minimum follow-up of 2 years). Two of these patients died of their head and neck tumour with no further evidence of a lung neoplasm.

An interesting finding was that, of the 19 positive bronchial washings, 10 patients had a carcinoma of the larynx and two had a large (T3 and T4) hypopharyngeal carcinoma Two of the 11 patients with bilateral bronchial washings that had been considered as contamination at the time of diagnosis, developed a lung carcinoma: one after 8 months and the other after 15 months.

Table 1 : Patients with a known primary tumour of the head and neck with a unilateral positive bronchial washing.

Date of birth (d/m/y)	primary	TNM	BW-R*	BW-L*	RX and/ or CT chest	Survival
30 07 39	161	3.1.0.	5	2	CT chest nl	alive at 10/94 > 27 months
09 03 22	161.0	2.0.0.	5	2	RX chest nl	alive at 10/94 > 36 months
31 07 48	161.0	2.0.0.	3	5	CT chest nl	alive at 10/94 > 40 months
10 10 25	141.0	4.0.1.	5	3	CT chest abno	dead(suicide) 16 days
01 02 14	161	3.2.1.	2	4	RX chest nl	alive at 10/94 > 28 months
29 06 27	150	4.0.0.	5	2	CT chest abno	dead 2 1/2 mont
19 11 23	148	4.2.0.	3	5	RX chest nl	dead of primary 10 months
25 03 56	144.0	3.1.0.	2	5	CT chest nl	dead of primary 8 months

T= tumour; BW= bronchial washing; R= right; L= left; nl= normal; abno= abnormal; RX= chest radiograph; CT= computerized tomography.

* *Papanicolau Class*

DISCUSSION

There is still a lot of controversy concerning the value of bronchial cytology in the detection of a lung neoplasm in the presence of a known head and neck carcinoma, especially if the cell type is similar. When looking at different studies, the contradictory results are partially explained, in our opinion, by differences in technique and the characteristics of the population examined.

Garfinkle et al. performed flexible bronchoscopy on 107 patients with head and neck cancer (2). In about half of the cases, the bronchoscope was passed through the endotracheal tube, whereas the bronchoscope was passed adjacent to the endotracheal tube in the remaining cases. Two patients were found to have a lung neoplasm. Thirteen patients (13%) had false-positive bronchial washings. Most of these patient's primary tumours were located in the larynx. An interesting finding was that the majority of the false-positive washings (10/13) occurred when the bronchoscope was passed adjacent to the endotracheal tube when compared with the technique in which the bronchoscope was passed through the tube. Denneny et al. performed a flexible bronchoscopy in 150 patients with a primary carcinoma of the head and neck (6). The majority of the bronchoscopies were performed through an endotracheal or tracheotomy tube. There was no information about the site of the index tumour. Four patients were found to have concomitant primary lung neoplasms; they reported no false-positive cytology result in their series. Dellon et al. found no false-positive cytology results in a series of 18 patients with head and neck cancer who underwent flexible bronchoscopy with bronchial washings under local anaesthesia (4). Johnson et al. reported only one false-positive cytologic result from a bronchial washing in a series of 100 patients with a head and neck cancer (3). They performed rigid bronchoscopies, and half of their population had a laryngeal carcinoma.

Our results confirm the observation of Garfinkle et al. In our study, contamination of bronchial washings with tumours cells from head and neck neoplasms did take place and seriously limited the usefulness of positive bronchial cytology. The assumption that we made about bilateral positive bronchial washings being due to contamination is possibly also not valid, because 2 of the 11 patients did develop a lung carcinoma. The majority (8/13) of the patients with false-positive bronchial washings in both the study by Garfinkle et al. and in ours (10/17) are patients with laryngeal cancer. This probably explains why Dellon et al. found no false positive bronchial washings in their small series of 18 patients. Most of the head and neck tumours did not lie in proximity to the path of the bronchoscope (8/18 oral cavity carcinomas and only one laryngeal carcinoma). It is also evident that the larger the tumour, the more likely contaminationcan occur in the tracheobronchial tree.

Most authors agree that shedding of malignant cells from the head and neck primary into the tracheobronchial tree is unusual. (2,3,4,11) Malignant cells desquamate but

are cleaned by mucociliary transport that goes upwards. However, contrary to previous reports, contamination of the bronchial washings with malignant cells from the head and neck primary tumour can occur in those situations when the bronchoscope, rigid or flexible, is passed through the larynx adjacent to the endotracheal tube in close contact with the tumour. False positive cytology findings occur most commonly in cases of carcinoma of the larynx, so contamination of the bronchial washings is probably attributable to direct contact of the bronchoscope and the tumour. Passage of the flexible fiber-optic bronchoscope through the endotracheal tube avoids mechanical contact with the tumour and provides more reliable cytologic specimens.

CONCLUSION

The incidence of simultaneous primary lung carcinomas is low, therefore, we believe that the sensitivity and specificity of the rigid bronchoscopy with bronchial washings is too low to justify its use. The use of the flexible bronchoscope seems to be superior for examining the lung for possible malignant lesions. First of all, it can be passed through the endotracheal tube and, therefore, enables bronchial washings to be performed without traumatizing the head and neck tumour. Second, it enables visualization of peripheral bronchial segments up to the fourth and fifth order, and washings can be isolated from specific segments. Flexible instrumentation also allows better evaluation of the upper lobe.

Additional techniques have been developed to augment the sensitivity of bronchoscopy, such as fluorescence bronchoscopy using fluorescing drugs that are preferentially retained in tumours (7) or the recent use of autofluorescence intensity in areas with dysplasia or carcinoma in situ, compared to normal bronchial tissue, using a helium-cadmium laser (442 nm) for illumination (8,9,10).

As most of the lung tumours occur metachronously in the first 2 years after diagnosis of the primary tumour, even the use of a flexible bronchoscope as a routine screening procedure in head and neck cancer patients with a normal chest X-ray film is still open for discussion. Perhaps the greatest value of the flexible bronchoscope lies in its use for the follow-up of head and neck cancer patients.

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CHAPTER 6

MULTIPLE PRIMARY MALIGNANT TUMOURS IN PATIENTS WITH HEAD AND NECK CANCER : RESULTS OF A PROSPECTIVE STUDY AND FUTURE PERSPECTIVES

Multiple primary tumours in patients with head and neck cancer: results of prospective study and future perspectives.
IJ Dhooge, M De Vos, PB Van Cauwenberge
The Laryngoscope: accepted

ABSTRACT

Multiple primary tumours are a known phenomenon in head and neck cancer. They are partially responsible for the limited improval in survival of head and neck cancer during the last 20 years. Only a few prospective data have been published about the incidence of metachronous tumours. We prospectively studied 127 patients with squamous cell carcinoma of the head and neck. The overall incidence of second primary tumours was 13.5% (simultaneously = 3%, synchronously = 5.5% and metachronously 8%). More then 90% of the recurrences of the first primary tumour occurred within the first two years following primary treatment, but the second primary tumours continued to occur gradually in the course of follow-up. Most of the second primary tumours were discovered because the patients developed symptoms (14/17). Survival after detection of the second primary tumour was poor. The development of a second primary tumour was of equivalent prognosis than a recurrence of the primary tumour. Future directives are the development of more adequate screening methods. Identification of potential early markers for the development of a squamous cell carcinoma at the level of the mucosa at risk, and in serum could be of value for the early detection of individuals at risk. Chemoprevention is another promising tool in the prevention of development of second primary cancer.

INTRODUCTION

Squamous cell carcinoma of the upper aerodigestive tract is known to be frequently associated with a second primary carcinoma. A series of retrospective studies have been published giving incidences of second primary tumours varying from 5% to 30%. This knowledge resulted in prospective studies looking for synchronous and metachronous multiple primary tumours. As was expected, in prospective studies, incidences of synchronous tumours were even higher. However, only a few prospective data have been published about the incidence of metachronous tumours (Table 1).

Table 1. Incidence of synchronous and metachronous multiple primary tumours in squamous cell cancer of the head and neck (prospective studies only)

FirstAuthor (reference)	year	location	n	Second primary synch	metachr	total	follow-up (in months
Weaver (1)	79	Michigan	124	13%	7%	20%	24
Atkinson (2)	82	Michigan	271	10.3%	15.1%	25.5%	58
Atkins (3)	84	Philadelph	451	2.5%	8.5%	11%	120
Choy (4)	91	Hong Kong	573	1.9%	0.5%	2.4%	22 (mean)

n : index tumour cases

Demographic variations in patterns of head and neck malignancies imply that the incidence of multiple primary tumours published in literature cannot unquestionable be extrapolated to different countries. Therefore we conducted a prospective study of patients with head and neck malignancies undergoing treatment and follow-up at the Department of Otorhinolaryngology at the University Hospital of Ghent.
The aims of the study were:
1) To quantify and characterize the problem of multiple primary malignancies.
2) To look at the implications of the appearance of a second primary tumour on survival.
3) To derive guidelines for follow-up of patients with head and neck cancer.

MATERIALS AND METHODS

A detailed prospective analysis has been carried out of 127 consecutive, previously untreated patients with squamous cell carcinoma of the head and neck region referred to the Department of Otorhinolaryngology of the University Hospital of Ghent (Belgium), between October 1990 and October 1992. Only squamous cell carcinoma

of the oral cavity, the oropharynx, the hypopharynx, the larynx and the cervical esophagus were included. Patients with a malignancy of the skin, the paranasal sinuses, nasopharynx, salivary glands or thyroid were excluded. After treatment, follow-up visits were performed every three months. During the follow-up visits only a clinical examination of the upper aerodigestive tract was performed. Every year a standard X-ray of the chest. was taken. We did not routinely perform flexible esophagoscopy or bronchoscopy. We had a minimum follow-up of 24 months. In this analysis, we specifically looked for recurrences of the index tumour and the appearance of second primary tumours in the upper aerodigestive tract and the lung. To define a second primary tumour Warren and Gates criteria modified by Hong were used (5,6). These criteria require that 1) both tumours are histologically malignant, 2) they must be separated by at least 2 cm of normal, healthy mucosa, 3) the possibility of the second tumour representing a metastasis must be excluded.

The original presenting tumour, which brought the patient to examination, was termed the index tumour. During the follow-up period, all lesions which occurred at the same site or direct vicinity (<2 cm) of the index tumour were considered as recurrences.

The tumours were also classified according to their temporal sequence as formulated by Moertel (7). Synchronous tumours included those that presented either simultaneously or within a 6 months period of identification of the original tumour. Metachronous tumours were identified as tumours diagnosed more than 6 months after the index tumour.

The site and subsites of the head and neck were defined according to the criteria of the International Union Against Cancer (UICC) and the International Classification of Diseases for Oncology (ICD-O) (8). In case a tumour involved more than one (sub)site, we retained the (sub)site in which the bulk of the tumour was localized. Regarding the tumour size and lymph node involvement, all tumours were coded according to the latest UICC TNM classification (8).

At the initial diagnosis, a panendoscopic examination was performed in every patient to look for simultaneous primary tumours. The results of this procedure have been described elsewhere (9). The follow-up has been described in person-years of follow-up. The number of years at risk of a second primary tumour was calculated until the date of the diagnosis of the second primary tumour, until October 1995, until the patient's death or the date of the last follow-up visit, whichever occurred first.

STATISTICAL ANALYSIS

Survival analysis was conducted using Kaplan-Meier estimates. Cox proportional hazard models were fitted to estimate risks of death or tumour relapse adjusted for age and sex. All statistical tests were two-sided.

RESULTS

1. General

127 patients with a newly diagnosed head and neck malignancy, admitted to the Department of Otorhinolaryngology of the University Hospital in Ghent between October 1990 and October 1992, were included in the study. This group consisted of 116 men and 11 women (male to female ratio : 10 to 1). The median age for the men was 59 years and for the women 58 years. By the time of the record review (October 1995), 86 patients (68%) were still alive. We had a total of 354,5 person-years of follow-up. The mean follow-up time for the whole group was 30 months (1-77 months).

2. Site and stage distribution of the index tumour

The site and stage distribution of the different index primaries is given in Table 2. Half of the patients had laryngeal cancer; 26 glottic carcinomas, 18 supraglottic carcinomas, 18 transglottic carcinomas and 2 subglottic carcinomas. Smoking and alcohol habits of the patients are described elsewhere (10).

Table 2. Site and stage distribution of the index primaries of 127 patients

Index primary site	n	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
oral cavity	14	-	-	4	4	6
oropharynx	35	2	7	5	12	9
hypopharynx	11	1	1	4	2	3
larynx	64	-	7	17	15	25
oesophagus	3	-	-	-	-	3
Total	127	3	15	30	33	46

n : number of patients

In terms of initial therapy, 117 patients were treated with a curative option and 10 patients with a palliative intent. The treatment of the index tumour is given in Table 3. Seven patients (5.5%) were lost to follow-up. Forty patients developed a recurrence of their primary tumour (31%) and 17 patients developed a second primary tumour

(13.5%), either simultaneously (3%), synchronously (5.5%) or metachronously (8%). Time to tumour relapse (= recurrence or second primary) is represented in figure 1.

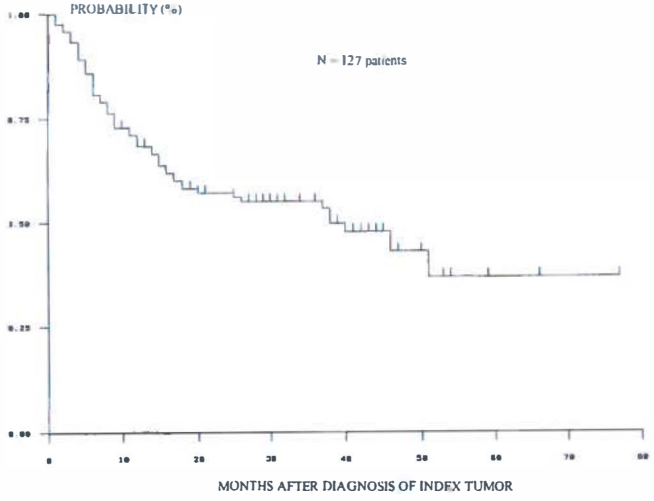
Table 3. Initial therapy of 127 patients with head and neck carcinoma

Curative	117
Palliative	10
Radiationtherapy	62
Surgery/radiationtherapy	34
Surgery	14
Chemotherapy/radiation therapy	13
Chemotherapy/surgery/radiation therapy	3
Chemotherapy	1

Median time to first relapse was 40 months. Age and gender were not predictors of tumour relapse : p values derived from Cox model were of 0.31 for age, and 0.73 for gender.

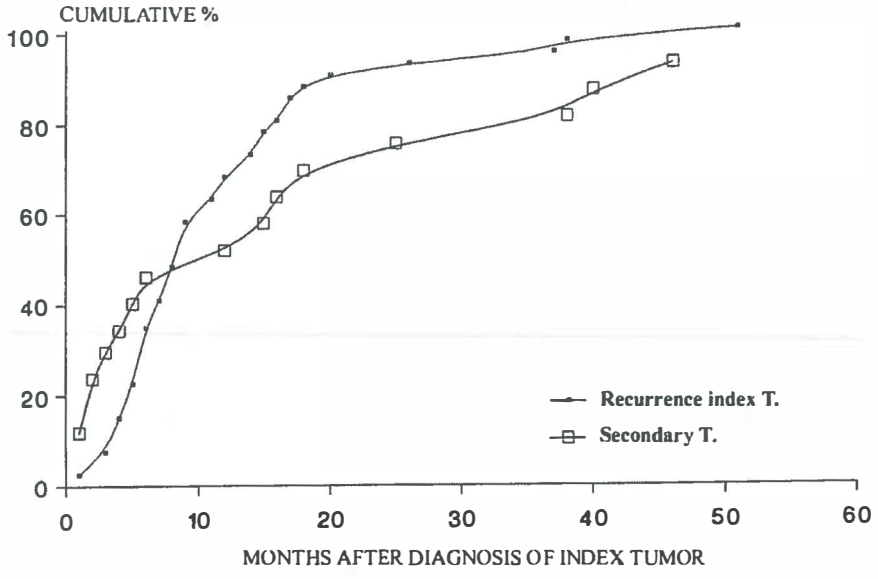
Figure 2 shows the time to recurrence of the index tumour or occurrence of second

Fig. 1. Time to first tumor relapse



primary tumour. In our series 90% of the recurrences of the first primary tumour occurred within the first two years following primary treatment; thereafter we reached a saturation point. For the occurrence of second primary tumours, we saw a steep rising cumulative distribution function during the first months but they continued to occur gradually in the course of follow-up.

Fig. 2. Time to recurrence of index tumor or occurence of second primary tumour



3. Symptoms leading to diagnosis

In the majority of the patients (72%), the diagnosis of recurrence was made during the scheduled follow-up visits. Often the patient reported suggestive symptoms or signs during this visit. Also, most of the second primary tumours were discovered because the patients developed symptoms (14/17). In 3/17 cases the asymptomatic tumour was found because of the routine radiographic examination of the lungs during follow-up. All patients with second primary tumours in the esophagus had symptoms.

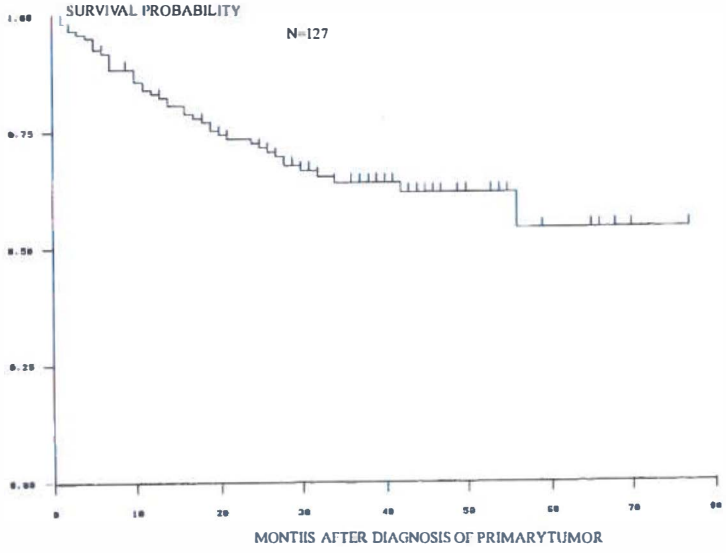
4. Incidence and location of second primary tumours

The incidence and location of the second primaries for the four different sites are given in Table 4. The most frequent sites of development of a second malignant tumour were the lung (41%) and the head and neck region (35%). Esophageal second primary tumours occurred in 24% of the cases. Of the second primary tumours, all the esophageal and 6/7 lung tumours were advanced stages of disease and treated with palliative intent. Five of the 6 head and neck second primary tumours were stage 1 tumours.

5. Survival

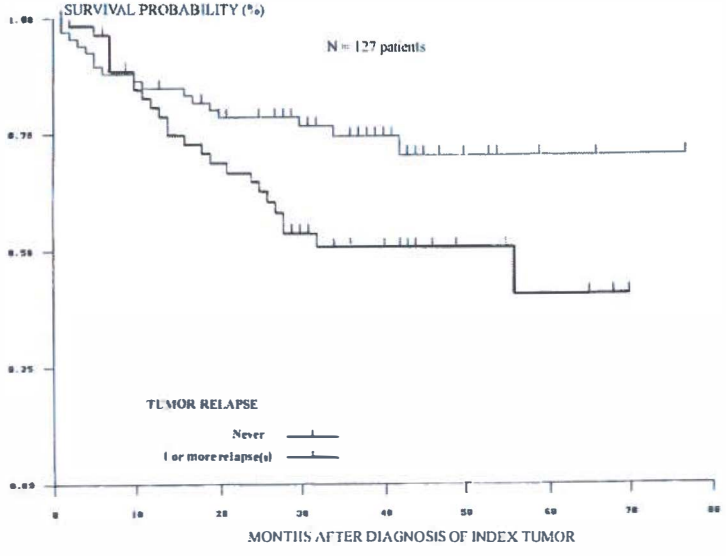
Overall survival is shown in Figure 3. 75% median survival is 20 months. Patient's age (p=0.69) and patient's sex (0.76) did not influence the survival.
As shown in Figure 4, 75% median survival decreased substantially to 14 months in

Fig. 2. Survival analysis for all patients



case of tumour relapse.
Table 5 displays results from Cox regression model including age, gender and tumour

Fig. 4. Survival analysis according to relapse



relapse. Evidence of tumour relapse was significantly associated with shorter survival. Risk of death was approximately two times higher for patients with relapse as compared to patients without a relapse.
The survival of the group of patients developing a recurrence of the index tumour was

Table 5. Cox regression of survival data (N = 127 patients). Hazard rates are adjusted for all factors

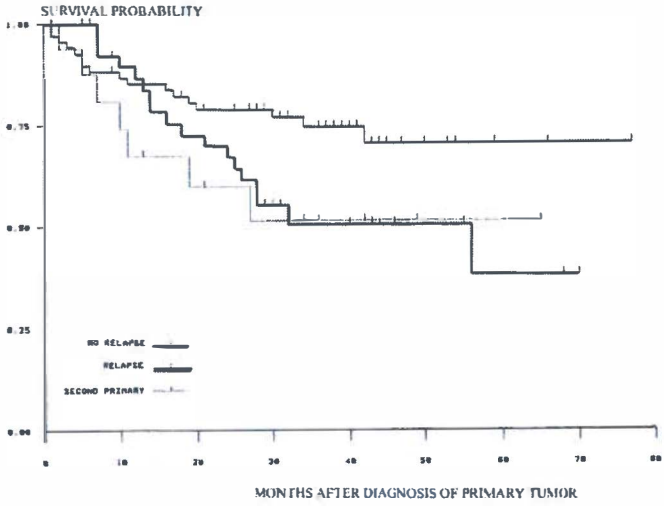
Factor	Adjusted Hazar Rate	95% Confidenc Interval	p value
Relapse or second prim tumour (never/ever)	2.0	1.1-3.7	0.029
Sex Female	0.9	0.3-2.4	0.76
Age (continuousvariable)	1.0	0.9-11	0.69

compared with the survival of those developing a second primary tumour (Figure 5 and Table 6). As shows fig 5, data censoring was well balanced between observed groups, hence, biases in length of follow-up due to severity of disease is not likely to have been present in this data set. Although the decreased size of patients in each strata lowers the power of the analysis, the development of a second primary tumour seems of equivalent prognosis than a recurrence of the primary tumour. Of the 17 patients who developed a second primary tumour, 7 died as a result of their second tumour. For those patients who died as a result of their second primary cancer the mean survival from diagnosis of second tumour to death was 7 months (0-16 months).

Table 6. Cox regression of survival data (N = 127 patients)

Factor	Adjusted Hazard Rate	95% Confidence Interval	p value
Recurrence	1.9	1.0-3.7	0.59
Second primary tumour	2.3	0.9-5.6	0.078
Sex Female	0.9	0.3-2.4	0.76
Age (continuous variable)	1.0	0.9-1.1	0.69

Fig. 5. Survival according to recurrence or second primary tumor



DISCUSSION

The occurrence of second primary tumours and its impact on survival has received much attention in the last 15 years. This phenomenon is especially important in head and neck cancer because it has been shown that patients with head and neck cancer have a greater risk of a second primary malignancy than any other group of patients with cancer (11,12,13). The incidence of 13.5% of second primary neoplasms is in accordance with the literature (Table 7) (14). In this study as well as in most follow-

Table 7. 5-year second cancer incidence between subgroups based on the site of index tumour (based on Schwartz et al. 1994 (14))

Index tumour	mobile tongue	base of tongue	oral cavity	tonsillae	pyriform sinus	larynx
Incidence SPT	10%	46%	18%	15%	34%	23%

up studies, we see that the majority of the recurrences of the index tumour occur within 2 years of initial diagnosis but there is, however, a constant and continuing risk of second primary tumours all over the years that follow initial treatment, varying from 2.7%/year to 4%/year depending on the site of the index tumour (15,16,17,18). After 36 months the appearance of a second primary carcinoma is the most common cause of failure (18,19,20). After 5 years of follow-up the chance of death from a second cancer is more than twice the risk of death from the index tumour (18,19,20). So the follow-up should shift away from the detection of local recurrence towards the detection of a second primary once the patient has survived 3 or 4 years after a primary head and neck carcinoma and this should be continued for long periods, if not lifelong.

Our study suggests that the impact of a second primary cancer on survival equals that of a recurrence of the primary tumour. Other studies confirm the bad prognosis once a second primary tumour has developed (18,20,21,22). The reasons for this poor outcome are multiple: the poor prognosis of esophageal and lung tumours, late diagnosis due either to inadequate initial evaluation or insufficiënt follow-up, and the inability to effectively treat the second tumour because of the effect of prior therapy for the first neoplasm.

In this context, early detection and chemoprevention strategies appear presently the best options to reduce morbidity and mortality related to multiple primary cancers. There is abundant literature on the extent of the initial diagnostic workup of the head and neck cancer patient to look for simultaneous primary tumours. However, very little is written about the follow-up examination of these patients. At present, most authors recommend annual chest roentgenograms in addition to regular physical examinations. This study shows that the regular follow-up visits have their greatest merit in the detection of second primary tumours located in the head and neck region, often helped by the fact that most of the patients at that time already developed symptoms. Also all esophageal second primary tumours as well as the majority of the lung tumours were diagnosed in an advanced stage of disease. Considering second primary lung tumours, yearly chest X-ray examination is clearly not sufficient as a screening for second primary lung tumours. This finding agrees with the findings of Engelen and with the disappointing results in general of population screening for lung cancer (23,24,25). In a study performed by Rachmat et al. the value of twice yearly bronchoscopy and sputum cytology in the follow-up of patients with laryngeal cancer was evaluated. They concluded that it was not useful as a routine procedure (25). So the question remains how frequently patients should be seen and how thorough the examinations should be at each follow-up visit. A logical approach would be to tailor the screening procedures in each individual case to the degree of risk for the development of second primary cancer. Early detection however, will be worthwhile only if effective treatment options exist for the tumours that are found. In case of a second primary tumour this is not always evident because of prior treatment of the index primary. Another method for influencing the survival of head and neck cancer patients is prevention of the development of a second cancer. It has been estimated that dietary and smoking habits contribute to at least 70% of all cancer deaths (26). Although smoking is a major risk factor in the development of initial primary cancer of the head and neck and the lung, it is still controversial whether stopping smoking once cancer is diagnosed affects the risk of second primary tumours (6,13,14,27,28). The occurrence of a second cancer early in follow-up suggests that the smoking and drinking habits of most patients prior to the appearance of the index tumour play a primary role in further tumour occurrence. The mucosa has been primed and retains a malignant potential (29,30). Avoidance of tobacco and alcohol is however a

desirable way to reduce the risk of second cancers of the aerodigestive system among long term survivors (28,31,32). Much research is currently being done to estimate the value of chemoprevention. Chemoprevention relies on the ability of certain chemical agents to block mutagenesis and control cellular differentiation and proliferation in epithelial tissues and therefore intervene in the process of carcinogenesis. Previous epidemiologic studies have linked the intake of certain micronutrients with a lower risk of cancer. Examples include vitamin E (alpha-tocopherol), beta carotene and vitamin A (33,34). Some experimental studies confirmed these findings. Gridley and Trickler showed that vitamin E supplementation may be effective in inhibiting oral cancer (35,36). A randomised trial of 13-cis retinoic acid in patients with oral leukoplakia revealed that it was able to cause significant decreases in the size of the leukoplakic lesions and to reverse dysplasia (13,34,37,38,39). In 1990, Hong et al. demonstrated that second primaries could be successfully prevented by the administration of 13-cis retinoic acid (6). Multi-institutional large-scale studies were started to investigate the use of different chemopreventive agents in the prevention of second primary cancers in patients treated for head and neck and/or lung cancer (6,27,34,40,41). Retinoids, which include natural vitamin A (retinol) and its esters and synthetic analogues, are the best studied class of agents in chemoprevention. In head and neck cancer, the clinical phase III trials in chemoprevention of second primary tumours have shown discordant results related to the type of retinoic acid. The results of the "Alpha-Tocopherol, Beta carotene Lung Cancer Prevention Trial", where a daily supplementation with placebo, alpha-tocopherol, beta carotene or both was given to a population of male smokers as a prevention trial, showed no reduction in the incidence of lung cancer among male smokers after five to eight years of dietary supplementation with alpha-tocopherol or beta carotene. The results of this study even raised the possibility that these substances may have harmful effects as they found an 18% increase in lung cancer in the group of male smokers who took 20 mg of beta carotene daily for 5 to 8 years (42). Also two large-scale American studies could show no beneficial effect of beta-carotene or the association of beta carotene with vitamin A in preventing cancer, cardiovascular mortality or any type of death (43). The investigators heading the beta carotene and retinol efficacy trial, known as CARET found a 28% increase in lung cancer in the group of participants taking a combination of beta carotene and vitamin A (43). This demonstrates that great care should be taken when interpreting results of epidemiological studies. Retinoids treatment should until now only be performed in control studies because of the toxicity at high doses.

Helpful in both, early detection and chemoprevention of second primary tumours, would be the identification of high risk individuals. In the past decades attempt have been made to isolate subgroups of patients at high risk. Heavy smokers and drinkers, especially those who continue these habits after treatment of their index tumours have

been found to be at increased risk for the development of second primary cancers (28,32,40,44). In some studies it has been shown that the prevalence and the localisation of a second primary tumour depends on the site of the index tumour (45). In addition, some analyses showed that male sex was an additional risk factor for the development of a second primary (20,23). Other studies could not find a statistically significant effect of variables such as index site, tumour stage and age at index diagnosis in predicting the appearance of a second primary cancer (16,20). Besides the known exogenous risk factors like smoking and alcohol consumption, endogenous constitutional factors also play a role in the development of head and neck cancer, since only a fraction of exposed individuals develops cancer (46,47,48). A positive family history for head and neck cancer and/or lung cancer is an independent risk factor for the occurence of a squamous cell carcinoma in the upper aerodigestive tract (48). While it has long been known that individuals with chromosome breakage syndromes are at increased cancer risk, evidence has been accumulating that cells derived from individuals developing some cancers exhibit increased radiation or mutagen sensitivity as detected by the G2 phase chromosome breakage assay when compared to cells derived from control individuals not bearing cancer (49,50). Mutagen sensitivity (defined as the mean number of breaks per cell (b/c) possibly reflects an individual's sensitivity for DNA damaging agents. Moreover, it has been shown that individuals who develop multiple head and neck primaries demonstrate the greatest degree of mutagen sensitivity in their lymphocytes (47). Intrinsic susceptibility and exposure to carcinogens increase cancer risk in a dose dependent and interactive pattern (51,52,53). Therefore, to investigate cancer susceptibility, classical epidemiology using only environmental exposure data is no longer adequate and requires the incorporation of endogenous constitutional factors. Chromosome breakage assay might therefore be of use in identifying these high-risk individuals (47,54). Mutagen sensitivity in combination with smoking history can be used to identify those patients at highest risk for the development of multiple primary tumors and who can be targeted for more intense follow-up, behavioral interventions and chemoprevention studies (55,56). Different biomarkers are studied for their usefulness as markers for the prediction of second primary tumours. Some studies have shown that aberrant p53 oncoprotein expression seems to be an early event in the multistage process of head and neck multiple carcinogenesis and its expression in normal epithelium from head and neck cancer patients would indicate an increased risk for transformation to second primary cancer (57,58,59,60). Biomarkers which can be obtained with non-invasive techniques, would be of great value in screening and prevention in head and neck cancer patients. Biomarkers could also act as intermediate endpoints and would undoubtedly reduce time and cost currently required to conduct chemoprevention trials.

The best potential marker in exfoliated cells of the mucosa appears to be the histo-blood group antigen H type 2-chain. At the serum level Cyfra 21-1 is of possible value for monitoring response to therapy in head and neck cancer patients and early detection of recurrent disease. But in both cases, long term follow-up studies are necessary to evaluate the predictive value for the development of second primary tumours (46).

Future developments

1. Better knowledge of individual risk factors for the development of second primary cancer
2. More effective screening programs especially for the detection of lung and esophageal cancer should be developed and evaluated in prospective studies.
3. Further studies of potential early markers of carcinogenesis or establishing their value in predicting second primary cancer are necessary.

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CHAPTER 7

SUMMARY AND CONCLUSIONS
SAMENVATTING EN CONCLUSIES

SUMMARY AND CONCLUSIONS

The head and neck oncologists seem to be facing a complication with their success. Although an important reduction in local and regional relapses has been achieved, survival has not significantly increased during the last years. The occurrence of second primary tumours are partially responsible for this. In recent years, many reports were published reporting varying incidences of multiple primary tumours. Because most studies had only a limited number of patients, interesting observations were often not statistically significant. Therefore, an extensive review was performed on data from 25 studies reporting synchronous and metachronous second malignancies in head and neck cancer. This enabled us to have a better idea of the magnitude of the problem and to draw some statistically significant conclusions.

Based on these 25 reports, we found an overall prevalence of multiple primary tumours of 15.2%, which suggest a sufficient large yield to make screening worthwhile. Prospective studies showed a higher prevalence than retrospective studies. The prevalence and the localisation of second malignant tumours depended on the site of the index tumour. Oral cavity cancer showed the highest prevalence of second malignant tumours. Head and neck second primaries were most common in this group. Laryngeal cancer patients carried the highest risk for the development of a second primary in the lung. About half of the second primaries were detected within two years after the detection of the index tumour but they continued to appear even after 5 years. Second malignant neoplasms unquestionably influenced subsequent survival adversely. Possible improvement of the long-term survival of patients with squamous cell carcinoma of the head and neck could be achieved by more active control of second primary cancers. Several reports therefore recommended a more systematic search for additional primary lesions in all patients with newly diagnosed head and neck. As such, panendoscopy has been proposed by many investigators to search for simultaneous second primary malignant neoplasms in patients presenting with head and neck cancer.

To evaluate the usefulness of this procedure in a Belgian population with head and neck cancer, we conducted a prospective study of patients with head and neck malignancies undergoing treatment and follow-up at the Department of Otorhinolaryngology at the University Hospital of Ghent. During 24 months, every new, untreated head and neck cancer patients was entered in the study. We used standardised forms to gain information about tobacco and alcohol use at the time of diagnosis, the medical history concerning previous malignancies and the delay in referral. We performed a panendoscopic examination as a routine screening procedure at the initial evaluation of every head and neck cancer patient. More than half of the patients consulted our institution with an advanced stage of disease which shows a possible bias of the cancer population we see at the University Hospital.

Concerning nicotine and alcohol use, our results supported the hypothesis that tobacco smoking is more strongly associated with lesions in sites heavily exposed to inhaled smoke, whereas alcohol consumption has a stronger effect on structures belonging to the «food channel» and reservoir systems. Interestingly enough, we found a lack of association between delay of diagnosis and tumour stage at diagnosis. We found however a statistical significant correlation between the delay and the tumour site. Therefore we concluded that tumour stage at diagnosis is determined mostly by the intrinsic difference in tumour aggressiveness and not so much by the delay in diagnosis. The delay reflects the clinical phase of the tumour which varies from site to site rather than it reflects the behaviour of the patient.

Screening for simultaneous second primary tumours by means of the panendoscopy yielded an incidence of 3.4% of simultaneous second primary neoplasms. This is consistent with findings reported from the Netherlands but low compared to other series deriving mostly from the United States. This can partially be explained by a different way of collecting data, but possibly also confirms racial and environmental differences. Because of the low yield we do not support the use of panendoscopy as it is described in chapter 3, as a screenings procedure in every head and neck cancer patient. Concerning the esophagoscopy, there was no convincing evidence that esophageal screening during initial workup of head and neck cancer patients leaded to diagnosing smaller tumours with subsequent better survival rates. For the rigid bronchoscopy with bronchial washings as a screening procedure during the initial evaluation of a head and neck cancer patients, the same conclusions could be drawn. The incidence of simultaneous primary lung carcinomas was low and the sensitivity and specificity of the rigid bronchoscope too low to justify its use. Contamination of bronchial washings with tumour cells from the head and neck index tumour, limited seriously the usefulness of bronchial cytology. We supported only oro-hypopharyngo-laryngoscopy under general anesthesia as a screening procedure for evaluation of the entire mucosa of the oral cavity, oropharynx, hypopharynx and larynx in every patient with a squamous cell carcinoma of the head and neck, this based on the fact that, although the incidence of simultaneous primary cancers was low, the majority of the simultaneous primary tumours were located in the head and neck region.

There is abundant literature on the extent of the initial diagnostic workup of the head and neck cancer patient. However, very little is written about the follow-up examination of these patients. At our department, follow-up visits were performed every three months. As a screening procedure for second primary tumours, we performed a thorough clinical examination of the upper aero-digestive tract every three months. Every year, a standard X-ray of the chest was taken. We did not routinely perform flexible esophagoscopy or bronchoscopy. We specifically looked for recurrence of the index tumour and the appearance of second primary tumours in the upper aero-digestive tract and the lung.

As a result of a minimum follow-up of 24 months, we found an incidence of 13.5% of second primary neoplasms, either simultaneously (3.%), synchronously (5.5%) or metachronously (8%). The most frequent sites of development of second malignant tumours were the lung and the head and neck region followed by cervical esophageal cancer. In the course of follow-up, we saw a continuing risk of new primary tumours following initial treatment. Our study suggested that the impact of a second primary cancer on survival equalled that of a recurrence of the primary tumour. The outcome is often worse than the corresponding index tumours because second primary tumours arise frequently in bad sites, such as the lung and the esophagus or in previously irradiated or operated areas. This study showed that the regular follow-up visits had their greatest merit in detection of second primary tumours located in the head and neck region, often helped by the fact that most of the patients at that time already developed symptoms. Yearly chest X-ray examination is clearly not sufficient as a screening for second primary lung tumours. This finding agrees with the disappointing results in general of population screening for lung cancer.

Future directions

Early detection and prevention strategies appear at present, the best options to reduce morbidity and mortality related to multiple primary cancer.

For *early detection* of second primary cancers, more effective screening programs should be developed. Further efforts should be made to identify high risk individuals where more intense screening using more sensitive methods could have a higher yield. Up to date, our knowledge of risk factors is still fragmentary. Epidemiological studies could not find a statistically significant effect of variables as site or stage of the index tumour in predicting the appearance of a second primary cancer. The only patients who seem to be at low risk are those who did not smoke nor drink alcohol at the time of the first primary. Recent studies have shown that besides the known exogenous risk factors like smoking and alcohol consumption, endogenous constitutional factors play a role in the development of head and neck cancer. There is a genetically determined variability of enzyme systems important in the detoxification pathways of procarcinogenic components. Moreover, increased mutagen sensitivity shown in patients developing multiple primary tumours, could result from an inherited predisposition. Combination of exogenous and endogenous risk factors could lead to a selection of patients who will benifit most from cancer prevention and control.

A valuable tool in monitoring squamous cell carcinoma of the head and neck would be the development of tissue (mucosa) markers. A suitable biomarker has to meet several criteria. It has to be detectable in tissue samples that can easily and repeatedly be obtained from several sites of the aerodigestive tract in a non-invasive way. The best potential marker in exfoliated cells of the mucosa appears to be the histo-blood

group antigen H type 2-chain. At the serum level Cyfra 21-1 looks to be of potential value for monitoring head and neck cancer patients. But in both cases, long term follow-up studies are necessary to evaluate the predictive value for the development of second primary tumours.

Prevention of the development of a second cancer is a desirable objective. Dietary and smoking habits contribute to at least 70% of all cancer deaths. Although smoking is a major risk factor in the development of initial primary cancer of the head and neck, it is still controversial whether stopping smoking once cancer is diagnosed affects the risk of second primary tumours. The occurrence of second cancer early in follow-up suggests that the smoking and drinking habits of most patients prior to the appearance of the index tumour play a primary role in further tumour occurrence. Continuing efforts should however be made to motivate the patients to stop smoking and drinking, certainly in patients with a good prognosis.

Much research is currently being done to estimate the value of chemoprevention as an additional approach to improve the life expectation of patients with squamous cell carcinoma of the head and neck. Two drugs are momentarily intensively studied: the retinoids and N-Acetylcystein (NAC). Both have an antioxidant activity. It has already been shown that the use of high-dose isotretinoin is able to reduce leukoplakia and to prevent the development of second cancers. NAC is still an object of clinical research. Biomarkers could be of value in monitoring and evaluating the efficacy of chemopreventive agents and they could serve as intermediate endpoints.

Continuing efforts should be made to improve the understanding of the molecular events of the carcinogenesis process. The physician, engaged in the care of patients with cancer of the head and neck should be familiar with the concept of multicentricity. Careful vigilance should be exercised during the initial work-up and the follow-up period, not only for detecting recurrence but also to identify new primary cancers.

SAMENVATTING EN CONCLUSIES

Alhoewel we de laatste jaren een belangrijke vooruitgang hebben geboekt in de behandeling van plaveiselcelcarcinomen uitgaande van het slijmvlies in het hoofd-hals gebied, weerspiegelt zich dat niet meteen in een verbetering van de overleving van deze patienten. De ontwikkeling van tweede primaire tumoren is hiervoor deels verantwoordelijk. Om een beter inzicht te krijgen in de omvang van het probleem hebben we een meta-analyse verricht van data van 25 studies die in de loop der jaren zijn verschenen over synchrone en metachrone tweede primaire tumoren. De prevalentie van multipele primaire tumoren was 15.2%. Zoals verwacht vonden we een hogere prevalentie in de prospectieve studies. De prevalentie en de lokalisatie van de tweede primaire tumor is afhankelijk van de localisatie van de index tumor. De hoogste prevalentie werd gezien bij kanker van de mondholte. In deze groep was de voorkeurslokalizatie van de tweede primaire tumor in het hoofd-hals gebied. Patienten met larynx kanker lopen het grootste risiko om een tweede tumor te ontwikkelen in de long. Ongeveer de helft van de tweede primaire tumoren wordt gedetecteerd in de eerste twee jaar na de detectie van de index tumor. We bemerken echter dat zij met een relatief constante frequentie ook jaren na detectie en behandeling van de eerste tumor blijven voorkomen. Tweede primaire tumoren hebben over het algemeen een slechte prognose omdat zij ofwel op ongunstige plaatsen voorkomen (long en slokdarm), of in reeds behandeld gebied. Vroege detectie is een mogelijke optie ter vermindering van de morbiditeit en mortaliteit door tweede primaire tumoren. In die optiek is panendoscopie als screeningsmethode naar simultaan tweede primaire tumoren door veel auteurs geadviseerd gedurende de initiele evaluatie van een patient met een hoofd en hals tumor. Om een idee te krijgen over de incidentie van tweede primaire tumoren in onze populatie en panendoscopie te evalueren als screeningsmethode, werd er in Oktober 1990 gestart met een prospectief onderzoek bij patienten met hoofd en hals tumoren. Gedurende 24 maanden werd elke patient met een onbehandelde tumor van het slijmvlies van het hoofd-hals gebied, in de studie ingebracht. Er werd gebruik gemaakt van een gestandaardiseerd computerdossier (cfr addendum) om rookgewoonten en alcoholgebruik te registreren, de diagnose en behandeling van de index tumor te registreren en de follow-up van deze patienten bij te houden. Wat betreft het nicotine en alcohol gebruik in relatie tot de index tumor konden we besluiten dat het roken vooral is geassocieerd met letsels in die gebieden die sterk zijn blootgesteld aan de sigaretterook, terwijl het drinken van alcohol een sterker effect heeft op de voedselweg. Er was geen associatie tussen de periode van ontstaan van de klachten en de uiteindelijke diagnose («delay») en het stadium van de tumor. Er was wel een statistisch significante correlatie tussen het «delay» en de localisatie van de index tumor. Dit resultaat ondersteunt de hypothese dat het stadium van de tumor op het

moment van de diagnose vooral wordt bepaald door de intrinsieke biologische eigenschappen van de tumor, eerder dan dat deze het gedrag van de patient weerspiegeld. De incidentie van simultaan primaire tumoren in onze populatie bedroeg 3.4%. Dit is beduidend lager dan incidentie cijfers die we terugvinden in studies uit de Verenigde Staten. Dit kan deels te wijten zijn aan methodologische verschillen, maar reflecteert vermoedelijk ook raciale en omgevingsgebonden verschillen. Omwille van de lage incidentie in onze populatie, vinden wij het screenen d.m.v. een panendoscopie zoals we die hebben beschreven, bij elke patient met een hoofd-hals tumor, niet zinvol. De incidentie van simultane longtumoren is laag. Daarbij komt nog dat de gevoeligheid van de rigide bronchoscopie met bronchiale washing laag is. Gebaseerd op de vaststelling dat de meerderheid van de simultaan primaire tumoren gelokaliseerd zijn in het hoofd-hals gebied, adviseren wij, bij de initiele evaluatie van een patient met een tumor in het hoofd-hals gebied, enkel een oro-hypopharyngoscopie. Dit niet alleen ter evaluatie van de index tumor maar als screeningsmethode voor detectie van simultane primaire tumoren.

Na de diagnose en de behandeling van de index tumor, werden de patienten 3-maandelijks terug gezien op controleraadpleging. Elk jaar werd een thorax foto aangevraagd. Er gebeeurde verden geen screening d.m.v. bronchoscopie of oesophagoscopie. Na een minimum follow-up van 24 maanden, vonden we een incidentie van 13.5% van multipele primaire tumoren, waarvan 3% simultaan optraden, 5.5% synchroon en 8% metachroon. De tweede primaire tumoren waren het meest frekwent gelokalizeerd in de long en de hoofd-hals regio. Het verschijnen van een tweede primaire tumor was even nefast voor de overleving als het ontwikkelen van een recidief. Deze studie toonde ook aan dat een jaarlijkse thoraxfoto niet voldoet als screening naar tweede primaire tumoren in de long.

Toekomstperspectieven

Vroege detectie en preventie lijken op dit ogenblik de beste opties om de morbiditeit en de mortaliteit van tweede primaire tumoren in te dijken.

Voor vroege detectie is de ontwikkeling van een meer efficient screeningsprogramma noodzakelijk. De identificatie van individuen die een hoger risico lopen op de ontwikkeling van tweede primaire tumoren kan hierbij helpen.

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Tot op heden is onze kennis over risicofactoren nog onvolledig. In epidemiologische studies kon geen statistisch significant effect worden aangetoond van variabelen zoals lokalisatie of stadium van de index tumor of de incidentie van een tweede primaire tumor. De enige patiënten die blijkbaar een laag risico lopen zijn deze met een blanco nicotine en alcohol gebruik, op het ogenblik van detectie van de eerste primaire

tumor. Recente studies hebben aangetoond dat naast de bekende exogene risicofactoren zoals roken en alcoholmisbruik, ook endogene constitutionele factoren een rol kunnen spelen in de ontwikkeling van een hoofd en halstumor. Er bestaat een genetisch bepaalde variabiliteit van enzymesystemen die belangrijk zijn in de detoxificatie processen van procarcinogene componenten. Daarenboven is aangetoond dat een gestegen mutagene gevoeligheid in patiënten met multipele primaire tumoren vaak erfelijk bepaald is. Een combinatie van exogene en endogene risicofactoren kan ons helpen bij de selectie van patiënten waar intensief zal moeten worden gescreend naar het ontwikkelen van tweede primaire tumoren.

Een belangrijk hulpmiddel in het monitoren van epidermoïde epitheliomata van het neus-, keel- en oorgebied zou de ontwikkeling kunnen zijn van mucosale weefselmerkers. Een bruikbare biologische merker moet aan verschillende voorwaarden voldoen. Hij dient detecteerbaar te zijn in weefselspecimen die makkelijk en herhaaldelijk kunnen worden afgenomen van verschillende lokalisaties in de aerodigestieve tractus op een niet-invasieve manier. De beste merker in mucosale cellen lijkt de bloedgroep antigen H- type 2. In het serum lijkt Cyfra 21-1 potentiële waarde te hebben om patiënten met een hoofd-en halstumor te volgen. In beide gevallen echter zijn lange termijnstudies noodzakelijk om de predictieve waarde van deze merkers te bepalen in het kader van tweede primaire tumoren.

Een belangrijk objectief is de preventie van ontwikkeling van tweede primaire tumoren. Het is bekend dat voedings- en rookgewoonten een inbreng hebben in minstens 70% van alle overlijdens door kanker. Alhoewel het is aangetoond dat roken een belangrijke risicofactor is in het ontwikkelen van een plaveiselcelcarcinoom in het hoofd- en halsgebied, bestaat er nog steeds controverse over de vraag of het stoppen met roken een invloed heeft op het risico om een tweede primaire tumor te ontwikkelen. Het optreden van tweede primaire tumoren kort na het ontwikkelen van de eerste suggereert dat rook-en drinkgewoonten vóór het ontstaan van de indextumor een belangrijke rol spelen in de ontwikkeling van een latere tumor. Volgehouden inspanningen om de patiënten te motiveren te stoppen met roken en drinken van alcohol is uiteraard van het allergrootste belang ; zeker bij patiënten met een goede prognose na een eerste tumor.

Momenteel wordt er veel onderzoek gedaan rond de waarde van chemopreventie als een aanvullende benadering om de levensverwachting bij patiënten met epidermoïde epitheliomata van het neus-, keel-, oorgebied te verbeteren. Twee medicaties worden momenteel grondig bestudeerd : de retinoïden en N-Acetylcysteïne (NAC). Beiden hebben anti-oxiderende activiteit. Vroeger werd reeds aangetoond dat het toedienen van hoge dosissen synthetisch vitamine A in staat is om leukoplakiische letsels te reduceren en om ontwikkeling van tweede tumoren tegen te gaan. De activiteit van NAC wordt nu nog klinisch onderzocht. Biologische merkers kunnen een waarde hebben in het monitoren en het evalueren van het nut van chemopreventie.

Het is van het allergrootste belang nog meer inzicht te verwerven in de moleculaire processen die tijdens de carcinogenese plaatsvinden. De arts die te maken heeft met patiënten met een hoofd-en halstumor moet vertrouwd zijn met het concept van multi-centriciteit. Tijdens de initiële diagnostische oppuntstelling en tijdens de follow-up dient hij niet alleen zorgvuldig recidieven op te sporen maar ook bedacht te zijn op de ontwikkeling van secundaire primaire tumoren.

CURRICULUM VITAE

Ingeborg Dhooge werd op 28 december 1963 geboren in Eindhoven, Nederland. In 1980 behaalde zij het humanioradiploma richting Latijn-Wetenschappen aan het St-Andreas Instituut in Oostende. In 1981 begon zij de studie geneeskunde aan de Rijksuniversiteit van Gent, die zij in 1988 beeindigde. Vanaf augustus 1988, startte zij haar opleiding tot Neus- Keel- Oorarts bij Dr Geldof in het St-Lucasziekenhuis in Brugge. Na twee jaar werd haar opleiding verder gezet aan het Universitair Ziekenhuis in Gent bij Professor Van Cauwenberge. Gedurende die periode werd gestart met het onderzoek waarvan dit proefschrift het resultaat is. Op 31 juli 1992 werd zij erkend als Neus- Keel- Oorarts. Sindsdien is zij verbonden aan de dienst Neus- Keel- Oorheelkunde van de Gentse Rijksuniversiteit.

DANKWOORD

Zoals de behandeling van hoofd en halstumoren een nauwe multidisciplinaire samenwerking veronderstelt, is dit proefschrift ook het resultaat van de inspanningen van diverse mensen die direct of indirect betrokken waren bij het inspireren, het coördineren, het verwerken en interpreteren van dit werk. Mijn dank hiervoor.
In het bijzonder wil ik Prof. P. Van Cauwenberge en Prof. F.W.J. Albers, mijn promotoren, bedanken. Prof Albers lag aan de basis van dit proefschrift. Zijn wetenschappelijke ingesteldheid en zijn nooit aflatend enthousiasme maakten de start van dit onderzoek mogelijk. Ook later, na zijn benoeming tot hoogleraar in Groningen, bleef hij mij stimuleren om dit project tot een goed einde te brengen. Prof. Van Cauwenberge heeft mij van bij de aanvang van mijn opleiding tot KNO-arts steeds gewezen op het belang van wetenschappelijk onderzoek. Zijn steeds aanwezige interesse, zijn praktische raadgevingen en zijn morele steun zijn voor mij gedurende de jaren van verwezenlijking van dit proefschrift een belangrijk houvast geweest.
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Een bijzondere dankwoord gaat uit naar Lic. B. Vinck die met onnoemelijk veel geduld mij begeleid heeft in al wat informatica betreft zowel in de registratie als in de verwerking van de gegevens.
Tevens wens ik ook die mensen te bedanken die in de dagdagelijkse zorg van patienten met hoofd- en halstumoren betrokken zijn en door hun dagelijks werk en inzet de basismaterie hebben geleverd voor dit proefschrift.

Een dankwoord aan Dr. Autier, Dhr. J. Loontjens en Dhr. L. Niville die allen een steentje hebben bijgedragen aan dit project.

Een heel speciaal dankwoord voor mijn ouders en schoonmoeder, zonder wiens hulp ik nooit de tijd zou hebben gevonden om dit proefschrift te schrijven.
Luc, Samuel, Laurens en Arnaud, bedankt voor jullie aanwezigheid en begrip.

ADDENDUM

Data file used for the registration and follow-up of head and neck cancer patients in this study.

HOOFD- HALS ONCOLOGIE REGISTRATIE

PERSOONLIJKE GEGEVENS

Naam : .....
Voornaam : .....
Straat + n° : .....
Woonplaats : .....
Postn : .....
Telefoon : .....
Burg. Stand :
Naam echtgenoot : .....

Beroep : .....
Bedrijf : .....
Localisatie : .....
Ras : .....
Geslacht : ☐ Man ☐ onbekend ☐ Vrouw ☐ overig

Geboortedatum : .....
Adremanummer : .....

Verwijzende arts : .....
Huisarts : .....
Behandelende arts : .....
Afdeling : .....

Aanleiding tot diagnose :

☐ Tumorsymptomen
☐ Rontgenbevolkingsonderzoek
☐ Stageringsonderezoek
☐ Follow up onderzoek : kliniek
☐ Follow up onderzoek : Rx
☐ Follow up onderzoek : labo
☐ Follow up onderz. : flex. bronchosc.
☐ Onbekend

Indien stageringsonderzoek pos. :

☐ trachea-bronchoscopie
☐ brocho alveolaire lavage
☐ oesophagoscopie
☐ laryngoscopie
☐ hypo-oropharyngoscopie
☐ onderzoek mondholte
☐ nasopharyngoscopie
☐ halspalpatie

TOPOGRAFIE EERDERE TUMOREN :

	Topografie :	Jaartal :
Tumor 1 :	.....	.....
Tumor 2 :	.....	.....
Tumor 3 :	.....	.....

Hoeveelste maligniteit ? :

Duur van de klacht :

- ☐ geen klachten
- ☐ 0-3 maanden
- ☐ 4-6 maanden
- ☐ 7-12 maanden
- ☐ 12 maanden
- ☐ onbekend

	Identiteit	Geslacht	Topografie	Code
Familielid 1	.....	.....	.....	.....
Familielid 2	.....	.....	.....	.....
Familielid 3	.....	.....	.....	.....
Familielid 4	.....	.....	.....	.....

RISICOFACTOR

Rookgewoontes :
- ☐ nooit gerookt
- ☐ pijp
- ☐ sigaren
- ☐ sigaretten zonder filter
- ☐ sigaretten met filter
- ☐ onbekend

Rookstop :
- ☐ gestopt sinds > 2 jaar
- ☐ gestopt sinds > 1 jaar
- ☐ gestopt sinds < 1 jaar
- ☐ niet gestopt

Rookgewoontes sigaretten detail :
- ☐ < 10 pack year
- ☐ 10-20 pack year
- ☐ 20-30 pack year
- ☐ > 30 pack year

Alcoholgebruik :
- ☐ niet
- ☐ niet dagelijks
- ☐ 1 E/dag
- ☐ 2-4 E/dag
- ☐ 5-9 E/dag
- ☐ 9 E/dag
- ☐ onbekend

Alcoholstop :
- ☐ gestopt sinds > 2 j.
- ☐ gestopt sinds > 1 j.
- ☐ gestopt sinds < 1 j.

ANAMNESE II

Andere Riscofactoren :
- ☐ geen
- ☐ slechte mondhygiene
- ☐ na bestraling H.& Neck.
- ☐ Ebstein Barr virus +
- ☐ Precancerose
- ☐ afweerstoornis
- ☐ Auto Immuunziekte
- ☐ andere

Indien precancerose :

Mondholte + oesophagus :
- ☐ leukoplakie homogene type
- ☐ leukoplakie nodulaire type
- ☐ erythroplakie
- ☐ lichten planus

Larynx :
- ☐ dysplasie : graad I
- ☐ dysplasie : graad II

TUMOR ANAMNESE I

Incidentiedatum : .....

Diagnose gesteld door : .....

Is er eeen stageringsonderzoek verricht ? ☐ ja ☐ nee

Type van stageringsonderzoek :
- ☐ Totscopie
- ☐ subtotscopie
- ☐ laryngoscopie
- ☐ hypo-oropharyngoscopie
- ☐ onderzoek mondholte
- ☐ nasopharyngoscopie
- ☐ halspalpatie

Complicatie bij stageringsonderzoek : .....

PRIMAIRE TUMOR :

Tumorlocalisatie : ..... Unifocaal/multifocaal : .....

Links/Rinchts : ..... Ontsteking/Randreactie : .....

Voor/Achter : ..... Infiltratie :
- ☐ infiltraties in bot
- ☐ infiltraties in spier
- ☐ infiltraties in huid

Maximale doorsnede van de Tumer : ..... cm.

REGIONALE LYMFEKLIEREN :

Lymfeklieren palpapel : ☐ ja ☐ nee

in level : ☐ Level 1
☐ Level 2
☐ Level 3
☐ Level 4
☐ Level 5
☐ Level 6

Afmeting grootste klier : ..... cm.

:

Metastasen op Afstand :

metastasen : ☐ geen
☐ in de long
☐ elders
☐ in de long en elders
☐ onbekend

cTNM stadium :

formule : cT : .....: ....

HISTOLOGIE PRIMAIRE TUMOR

Morfologisch type :
☐ Plaveiselcelcarcinoom
☐ Adenocarcinoom
☐ Verruceus carcinoom
☐ Verruceus carcinoom
☐ Adenocystisch carcinoom
☐ Basalioom
☐ Melanoom
☐ Hodgkin
☐ Non-Hodgkin
☐ Anaplastische tumor
☐ andere

Differentiatie graad :
☐ Goed gedifferentieerd (Graad I)
☐ Matig gedifferentieerd (Graad II)
☐ Slecht gedifferentieerd (Graad III)
☐ Differentiatie niet gespecificeerd

Extensie : (insitu/invasief/metastase)
☐ Benigne
☐ Maligne primaire tumor
☐ Maligne metastase of secundaire locatie
☐ Maligne (onzeker:primaire tumor of metastase)
☐ dysplasie graad I
☐ dysplasie graad II
☐ dysplasie graad III

Maximale doorsnede : .....

Groeiwijze : .....

radicaliteit : .....

Infiltratie diepte : .....

Unifocaal/Multifocaal :.....

Ontstekingsreactie : .....

HISTOLOGIE REGIONALE LYMFEKLIEREN

Afmeting grootste lymfeklier : ..... cm

Kapseldoorbraak : ☐ geen kapseldoorbraak
☐ kapseldoorgroei rechts
☐ kapseldoorgroei links
☐ kapelsdoorgroei beiderzijds
☐ onbekend

	onderzocht	tumorpositief		onderzocht	tumorpositief
Level 1	.....	.....	Level 1	.....	.....
Level 2	.....	.....	Level 2	.....	.....
Level 3	.....	.....	Level 3	.....	.....
Level 4	.....	.....	Level 4	.....	.....
Level 5	.....	.....	Level 5	.....	.....
Level 6	.....	.....	Level 6	.....	.....

THERAPIE I

Therapie Opzet :
☐ Geen therapie
☐ Curatief
☐ Palliatief
☐ Onbekend

Initiele therapievolgorde : (binnen 3 maanden)
☐ Geen therapie
☐ Radiotherapie
☐ Chemotherapie
☐ chemotherapie
☐ chemo/radiotherapie
☐ chemo/chirutgie
☐ chemo/radio/chirurgie
☐ chemo/chirurgie/radio
☐ radio/chirurgie
☐ chirurgie/radio
☐ radio/evaluatie/radio
☐ radio/evaluatie/chirurgie
☐ chirurgie

OPERATIEVE BEHANDELING PRIMAIRE TUMOR :

Soort Operatie : .....

Datum operatie : .....

Macroscopisch radicaal : .....

Aanvullende resectie nodig ? ☐ ja ☐ niet nodig

Reconstructie :
- ☐ Directe sluiting
- ☐ Huidtransplantaties
- ☐ Transpositielap huid
- ☐ Transpositielap mucosa
- ☐ Gesteelde lap myocutaan
- ☐ Gesteelde spierlap
- ☐ Vrije lap
- ☐ Onbekend

OPERATIEVE BEHANDELING LYMFEKLIEREN :

Rechts

Datum : .....

Type dissectie :
- ☐ geen nekdissectie
- ☐ radicale nekdissectie
- ☐ gemodifieerd radicale nek dissectie
- ☐ supra omohyoidale nekdissectie
- ☐ posterolaterale nek dissectie
- ☐ laterale nek dissectie
- ☐ dissectie vh voorste nek compartiment
- ☐ uitgebreide radicale nekdissectie
- ☐ onbekend

Links

Datum : .....

Type dissectie :
- ☐ geen nekdissectie
- ☐ radicale nekdissectie
- ☐ gemodifieerd radicale nek dissectie
- ☐ supra omohyoidale nekdissectie
- ☐ posterolaterale nek dissectie
- ☐ laterale nek dissectie
- ☐ dissectie vh voorste nek compartiment
- ☐ uitgebreide radicale nekdissectie
- ☐ onbekend

RADIOTHERAPIE :

Startdatum : .....

Stopdatum : .....

Aantal Gray op tumor : .....

Aantal Gray op hals : .....

CHEMOTHERAPIE :

Opzet : ☐ Inductie chemotherapie
☐ Adjuvante chemotherapie
☐ recidief/ meta's op afstand

Regime :	startdatum	stopdatum	Respons
.....	.....	.....	.....
.....	.....	.....	.....

FOLLOW UP :

Behandelingscomplicaties : ☐ Geen complicaties
☐ Huidnecrose
☐ Fistel
☐ Dehiscentie
☐ Trombose V. Jugularis
☐ Nabloeding
☐ Pneumonie
☐ Myocardinfarct
☐ Chyluslek

Doodsoorzaak : ☐ door tumor (primair)
☐ door tumor (secundair)
☐ door andere oorzaak

Datum overlijden : .....

Ontslagdatum eerste behandeling :

Datum :	Status therapie :
.....	.....
.....	.....
.....	.....
.....	.....
.....	.....
.....	.....
.....	.....
.....	.....
.....	.....
.....	.....
.....	.....
.....	.....
.....	.....
.....	.....

VOLGENDE MALIGNITEIT :

Incidentite datum : .....

Topografie (ICD-O*) : .....

Histologie (ICD-O*) : .....

Rookgewoontes : ☐ gestopt sinds detectie primaire tumor

Rookgewoontes : ☐ gestopt sinds detectie primaire tumor
☐ ongewijzigd (cfr prim. tumor)
☐ > de helft verminderd sinds detectie primaire tumor

Alcoholgebruik : ☐ gestopt sinds detectie primaire tumor
☐ ongewijzigd (cfr prim. tumor)
☐ > de helft verminderd sinds detectie primaire tumor

OPMERKINGEN :

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